STROKE - IN - PROGRESS

A Prospective Study of One Hundred Five Cases

Richard Doud Bey

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A [illegible] study of the [illegible]

by

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THIS THESIS IS SUBMITTED TO THE FACULTY
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Department of [illegible]
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B.S., Beloit College, 1974

This thesis is presented to the Faculty
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CHAPTER I

INTRODUCTION

Ischemic strokes are often characterized by abrupt onset of symptoms of focal brain disorder, in a distinctive array, denoting the location of the lesion, followed by gradual, partial or complete recovery. In other instances, within hours of the initial ictus, there are increments of worsening in stepwise progression. The period of increasing disability has been called stroke-in-progress, progressing stroke, stroke-in-evolution, ingravescent stroke, etc. It is differentiated from completed stroke when symptoms and signs have been stable for 48 hours. The temporal boundaries of these divisions are arbitrary and sometimes morbidity increases even in cases of completed stroke. A number of mechanisms might explain these variations. The stuttering or progressive pattern of increasing impairment which characterizes stroke-in-progress, often reflects repetition of the elements responsible for the initial event, i.e., recurrent embolus, extension of thrombus or episodic perfusion insufficiency without vascular occlusion. Also, some progression is due to cerebral edema, and edema is recognized as a potentially fatal complication of large infarcts. The onset of swelling cannot with certainty be differentiated from extension of the infarct, on the basis of clinical evaluation. In addition, seizures and malfunction of other organ systems may contribute to neurologic impairment. The latter include CHF, cardiac arrhythmias, pneumonia, atelectasis; also, renal or hepatic insufficiency, inappropriate ADH activity, glucose and electrolyte abnormality and GU infection or septicemia. The effects of CNS sedatives or tranquilizers also need to be taken into account. When these conditions increase brain malfunction they complicate the recognition

of extension of the infarct or development of local edema.

Another element may be very important. Several investigators have identified chemical and structural changes consequent to ischemic brain infarction in animal models of stroke. These studies demonstrate that after cell membranes break down, abnormal amounts of dopamine, norepinephrine, serotonin, K+, various lipid fractions and other products of altered metabolism concentrate in the infarcted tissue. Some of these substances cause vasoconstriction, others increase blood clotting and by these effects may extend the area of necrosis. It is reasonable to assume that similar tissue changes take place in human strokes, and that in some instances these substances are responsible for progression. Their role in the production of edema has not been fully determined.

While the animal experiments do not reproduce human disease, they have opened an area for investigation that had not developed from clinical studies or post-mortem examinations. As details about the temporal course and local effects of these tissue changes are expanded they may have important application to patient care. These considerations are pertinent for a review of the incidence, patterns and mechanisms of progressing stroke.

CHAPTER 2

HISTORICAL PERSPECTIVE

Appendix I critically reviews the literature of the last 40 years discussing stroke-in-progress.(1-53) The temporal profile of evolving stroke has been studied for its diagnostic and prognostic significance. The time course has also been examined to better understand the pathophysiology of stroke; a variety of therapeutic modalities have been attempted to halt progression based on changing concepts of etiology.

Aring and Merritt described the diagnostic usefulness of documenting the temporal profile of an increasing cerebral deficit to differentiate hemorrhagic, thrombotic, and embolic strokes.(1) The stepwise or stuttering time course particularly characterized thrombotic stroke.(6,11,25,49,50) However, embolic stroke may rarely present with a similar type of onset.(14,37,49)

Analysis of the time course of progressing stroke has also been of special interest in the search for both short and long term prognostic indicators. In two early reports Millikan, _et_ _al_. suggested that the more rapid the evolution of deficit the worse the prognosis.(4,5) Carter more recently came to a similar conclusion.(30)

Several neurologists have examined the time course of stroke-in-progress for insight into the pathophysiological mechanism. Millikan, Siekert, and Whisnant noted that the progressing stroke typically follows a stepwise time course over many hours and occasionally days.(20) They speculated that advancing thrombosis and associated reduction of cerebral blood flow, failure of collateral circulation, and neuronal death may all be responsible to varying degrees for progression.

Focusing on the temporal profile of "ingravescent cerebral infarction," Carter noted that fully one third of the population with progressing stroke evolve between 19 and 24 hours after the onset of symptoms.(21) He suggested that evolution may represent a special stroke mechanism, perhaps, of propagating thrombosis, initiation of new thrombotic sites, or repeated distal embolism.(15,22) Adams, Torvik, and Fisher presented similar theories and added that TIA's and progressing stroke may represent a continuum.(25) More recently, Houser, et al. have reemphasized the role of distal embolism in conjunction with failing collateral circulation.(52) Marshall, however, suggested that edema may also play a major role in early progression.(51) Carter and Patel stated that old age and hypertension adversely affect the early prognosis.(48)

The differing theories as to the dynamics of evolution have led to a variety of clinical trials to interrupt progression. Conflicting reports have been published on the efficacy of stellate block,(3,4) anticoagulation,(13,15,16,25,28) carotid vessel surgery,(36) and steroid therapy.(48) In interpreting the results of these studies several authors have noted the difficulty of evaluating any therapy, since the spontaneous course of the process has been only vaguely characterized.(4,5,12,16,17,23,30,32) Millikan continued, "the variability of the clinical course of actively advancing thrombosis makes indispensible the observation of a group of untreated patients for comparison of results before final evaluation of such treatment."(20) As discussed in Appendix I, many of these studies characterized the time course of evolution by history only, as the patients came under medical observation days or even months after the occurrence of progression. Unfortunately, our current understanding of the temporal profile of stroke-in-progress relies on these retrospective studies.(e.g. 18,24,26,33,34,40,44,50)

CHAPTER 3

OBJECTIVE

Noting an apparent lack in the literature, a prospective study of acute thrombo-embolic strokes was established at the Veterans Administration Hospital, West Haven, Connecticut. This study was based on the premise that frequent, detailed and standardized clinical examinations and intensive care unit monitoring throughout the acute period in a large cross-sectional representation of patients who were receiving equivalent care might make it possible to identify the onset of progression, characterize its time course, and allow for analysis of causes, perhaps in time to initiate appropriate therapy and evaluate its effects on altering the natural history of the disease.

CHAPTER 4

CASE MATERIAL

Between 1972-1975 patients from the New Haven, Connecticut area with the initial diagnosis of acute stroke were accepted into the Stroke Study Unit intensive care facility. Patients came through the V A Emergency Room or in immediate transfer from the two community hospitals in a Sharing Program agreement. Informed consent was obtained from all participants. Therapeutic interventions were undertaken as deemed necessary in the judgment of the attending neurologist.

Only patients with the onset of symptoms clearly less than twenty-four hours before admission were accepted into the Unit. To avoid confusing the characterization of the temporal profile of evolving stroke, data from patients admitted in seizure, post-ictal, or in coma were excluded.

Records from 349 cases were obtained, including those of thirteen repeat admissions to the Unit. At initial examination or subsequent follow-up by the neurology staff, thirty-two case records were eliminated from this study; twelve patients had spinal fluid findings consistent with the diagnosis of hemorrhagic stroke--three of these patients came to autopsy where the diagnoses were confirmed. Five patients were found to have cerebral tumors on angiography or C T scan. In two patients the diagnoses were changed to hysterical paralysis. One patient's weakness was caused by a sciatic nerve lesion. One patient admitted to the Unit was in hypoglycemic shock, and another syncopal from the Shy-Drager Syndrome. Two patients had suffered head trauma. One patient's stroke was a complication of carotid artery surgery. Another had an air embolic stroke status-post placement of a central venous line. One had a stroke as the

complication of neurovascular syphilis. One patient had a hypotensive stroke following the rupture of an abdominal aneurysm. Finally, four patients suffered their cerebral deficits following radiologic contrast reactions.

Data were therefore available from 317 cases of spontaneous thromboembolic strokes. In the data collection and registry the records of four patients were incomplete, leaving 313 cases for examination. Among these, 105 cases of in-hospital progression were identified and form the basis of the thesis.

CHAPTER 5

METHODS AND DEFINITIONS

To identify progression a staff of nurses was additionally trained to perform neurologic examinations. They numerically graded each of five categories of brain activity, i.e. language, mentation, motor, sensory and visual functions. This was done strictly according to the examination and grading system detailed in Appendix II.

The Stroke Care Unit was equipped to monitor four channels of E.E.G. and E.K.G. continuously from each of four patients. Systemic B.P. could be obtained and recorded automatically at repeated intervals as often as required. Central venous pressure and end tidal CO_2 measurement and recording capability were included in each patient monitor but were not used regularly.

The graded neurologic examinations together with other clinical and laboratory data were recorded on a standard form six to ten times daily for each patient during a five to seven day period. The ratings of neurologic function were randomly checked for agreement across examiners and for consistency. It was concluded that significant change in clinical status was reliably indicated when there was a difference of fifteen percentage points in any one category or when abnormality in a category was added or deleted from the results of the previous examination. Worsening of clinical status by these criteria was the basis of denoting progression. When such a change was detected by the nurse examiners, the findings were confirmed or rejected by the attending physician. If it was determined that progression had occurred an attempt was made to establish the cause by correlating the general physical and neurologic findings with EEG, EKG,

B P and other laboratory data. The day of progression was noted with respect to the admission day being labeled Day 1.

The individual case records were then coded and all data transferred to keypunch cards for registry at the Yale Computer Center on an I B M 370 machine. Data were therefore easily retrieved as to the age and sex of each patient, and if and when in-hospital progression of signs was detected. Also available were the admission and subsequent systolic and diastolic blood pressure readings, the clinical neuroanatomical location of the lesion. Noted was the presence of any seizure activity or cardiac dysrhythmia during the acute period or other evidence of cardiac impairment. In the registry was any past medical history of diabetes mellitus, hypertension or stroke. Finally, for each case any in-hospital therapeutic intervention was also recorded, as well as the total length of the hospitalization.

Each patient was categorized in one of five "Admission Classes" based on the severity of his deficit at the hour of presention to the Unit. The deficit was quantified and followed by strict application of the neurological examination and scoring system detailed in Appendix II. Using this system five Admission Classes of increasing neurologic impairment were defined:

Class I--T.I.A.'s i.e. history of a focal neurologic deficit lasting less than 12 hours duration.

Class II--mental status score of 75-100 with other deficits mild to moderate (50-75).

Class III--mental status score of 50-75 <u>or</u> excessive aphasia score 50-75 <u>or</u> other deficits moderate to severe.

Class IV--mental status score 25-50 <u>or</u> aphasia score 25-50. Other deficits need not be evident.

Class V--mental status score 0-25 _or_ aphasia score 0-25. Other deficits need not be evident.

Routinely all patients' admission orders included: "1. bedrest (flat) 2. monitoring EEG, EKG, BP qh 3. monitoring neurologic status [as outlined in Appendix II]. 4. NPO 5. no Foley catheterization. 6. no sedation. and 7. laboratory work of CBC with differential, SMA-18, triglycerides, serology, and a urine analysis."

CHAPTER 6

STATISTICS

The stroke subpopulation (n = 105) of patients with progressing infarct deficits is categorized into a variety of well-defined groups based on history and clinical examinations. Selected groups are compared with respect to extension day as the quantitative variable. Differences among groups are evaluated by a one-way analysis of variance with unequal sample sizes. All comparisons are made among those groups which most nearly approximate the requirements of a one-way analysis of variance and its use of the F statistics. Large values of F in a given comparison indicate at least one of the groups is different from the others. In the present study comparisons are made at the .05 level of significance. Four of the patients had extension days of from 11 to 34 and are called 11, while one patient had an extension day of from 35 to 50 and is called 12. For the purposes of this study, this adjustment is inconsequential since these patients appear randomly among the groups selected for comparison.

The entire stroke population, those with progressing infarct deficits (n=105) and the remaining group (n=208), were also classified into a variety of categories on the basis of history and clinical examinations. These pairs of classifications are compared by the chi-square test of goodness of fit. The calculations throughout this paper are defined by the following formulae for the one-way analysis of variance with unequal sample sizes:

$SST = \sum_{i=1}^{K}\sum_{j=1}^{ni} (x_{ij} - \bar{x})^2$ i.e. total sums of squares

$SST = \Sigma\Sigma x^2_{ij} - T^2/N$ where $T = \Sigma\Sigma x_{ij}$ and $N = n_1 + n_2 + \ldots + n_k$

$SSB = \Sigma n_i (\bar{x}_{i.} - \bar{x})^2$ i.e. the sums of squares between groups

$SSB = \Sigma T_i^2/n_i - T^2/N$ where $T_i = \sum_{j=1}^{n i} x_{ij}$

SSE = SST - SSB i.e. the within sums of squares.

CHAPTER 7

RESULTS

The ages of the 313 total cases ranged from seventeen to ninety-seven years with a mean of 66.48 years (σ=11.70). Males comprised two-thirds of the total population with a mean age of 64.59 (σ=10.42). For the females the mean age was 70.60(σ = 13.28) which is significantly older ($F=19.89 > 3.84$ at .05 level). There was no statistical difference in the mean age of the 105 patients with progressing infarct deficits (P.I.D.; $\bar{x}_1$ = 67.2, σ,=11.39) compared to the 208 non-progressing cases (N.P.; $\bar{x}_2$=66.13), σ_2= 11.87; $F = .6007 < 3.84$ at .05 level).

Table I compares the non-progressing group with the group subsequently exhibiting progression with respect to the number of cases in each Admission Class defined on page 9 at the time of presentation to the Unit. As calculated by chi-square analysis, each group presented initially with the same spectrum of deficits:

TABLE I

ADMISSION CLASS (progressing group versus non-progressing group)

	I	II	III	IV	V	TOTALS
PID	7 (8.05)	26 (29.86)	36 (25.50)	25 (26.84)	11 (14.76	105
NP	17 (15.95)	63 (59.14)	40 (50.50)	55 (53.16)	33 (29.24)	208
TOTALS	24	89	76	80	44	313

$X^2 = 9.096 < 9.488$ with 4 d.f. at .05 level i.e. distributions <u>not</u> different.

Overall time course of progression: The day of admission is labeled "Day 1." Table II indicates that progression occurred in over 90% of the cases within the first week of admission. The mean day of progression was

at 3.61 days with a standard deviation of 2.60. Nearly one-half of the cases showed their progression in the first two days; one-third progressed on Day 2.

TABLE II

TOTAL STROKE SUBPOPULATION (n=105) OF CASES WITH PROGRESSING INFARCT DEFICITS

NUMBER OF CASES	DAY PROGRESSION NOTED
13	1
37	2
16	3
12	4
11	5
2	6
4	7
2	8
1	9
2	10
4	11
1	12

$\bar{x} = 3.6095$

$\sigma^2 = 6.75229$

$\sigma = 2.5985$

90.48% extended in 7 days or less.

Sex: Table III tabulates the day of progression for the two sexes separately. The sixty-nine males had a mean day of observed progression of 3.77 days. The thirty-six females had a mean of 3.31 days. These means are calculated to be without statistical difference.

TABLE III

DAY OF PROGRESSION BY SEX

MALES (69 cases)

#	Day
7	1
24	2
11	3
9	4
6	5
2	6
2	7
2	8
1	9
1	10
3	11
1	12

$\Sigma\, x_{1j} = 260$

$\Sigma\, x_{1j}^2 = 1482$

$\bar{x}_1 = 3.7681$

FEMALES (36 cases)

#	Day
6	1
13	2
5	3
3	4
5	5
2	7
1	10
1	11

$\Sigma\, x_{2j} = 119$

$\Sigma\, x_{2j}^2 = 597$

$\bar{x} = 3.3056$

$C = 379^2/105 \quad \text{or } 1368.0095$

$\Sigma\Sigma\, x_{ij}^2 = 2077$

$SST = 2077 - 1368.0095 \quad \text{or } 708.9905$

$SSB = 260^2/69 + 119^2/36 - C \quad \text{or } 5.0617$

$SSE = 708.9905 - 5.0617 \quad \text{or } 703.9288$

$$F = \frac{5.0617/1}{703.9288/103} \quad \text{or} \quad .7406 < 3.94 \ \text{at .05 level}$$

i.e. means <u>not</u> significantly different

Age: The 105 cases of stroke-in-progress were sub-classified into five arbitrary age categories. Table IV clearly shows that the majority of cases were in patients between ages sixty and eighty years old. Only six cases of progression were found in patients below age fifty, reflecting the rarity of ischemic stroke in the younger population.

Among all five age categories there was no statistical difference in the mean day of stroke progression with the range between 3.067 and 4 days.

TABLE IV
AGE CATEGORIES

<50 years (6 cases)		50-59 (18 cases)		60-69 (33 cases)		70-79 (33 cases)		80-89 (15 cases)	
#	Day	#	Day	#	Day	#	Day	#	Day
1 -	1	2 -	1	3 -	1	4 -	1	3 -	1
2 -	2	3 -	2	13 -	2	13 -	2	6 -	2
1 -	3	4 -	3	5 -	3	4 -	3	2 -	3
1 -	5	3 -	4	4 -	4	5 -	4	1 -	5
1 -	11	4 -	5	4 -	5	1 -	5	1 -	6
		1 -	8	1 -	7	1 -	6	2 -	7
		1 -	12	1 -	8	1 -	7		
				1 -	9	1 -	10		
				1 -	10	3 -	11		
$\Sigma x_{1j} = 24$		$\Sigma x_{2j} = 72$		$\Sigma x_{3j} = 114$		$\Sigma x_{4j} = 123$		$\Sigma x_{5j} = 46$	
$\Sigma x_{1j}^2 = 164$		$\Sigma x_{2j}^2 = 406$		$\Sigma x_{3j}^2 = 558$		$\Sigma x_{4j}^2 = 745$		$\Sigma x_{5j}^2 = 204$	
$\bar{x}_1 = 4.0000$		$\bar{x}_2 = 4.0000$		$\bar{x}_3 = 3.4545$		$\bar{x}_4 = 3.7273$		$\bar{x}_5 = 3.0667$	

$C = 379^2/105$ or 1368.0095

$\Sigma\Sigma x_{ij}^2 = 2077$

$SST = 2077 - 1368.0095$

$SSB = 24^2/6 + 72^2/18 + 114^2/33 + 123^2/33 + 46^2/15 - C$ or 9.3299

$SSE = 708.9905 - 9.3299$ or 699.6606

$F = \dfrac{9.3299/4}{699.6606/k00}$ or $.3334 < 2.48$ at .05 level i.e. means not significantly different.

Site of infarct: In 88 of the cases of progressing stroke the neurologic examination information was available to clearly localize the infarct into one of three broad areas: the right hemisphere, the left hemisphere, or the brainstem. Infarcts were twice as common in

either hemisphere than the brainstem and occurred with approximately equal frequency in either hemisphere. The time course of progression was statistically the same in all three locations as shown in Table V.

TABLE V

SITE OF INFARCT

CVA RT (33 cases) HEMISP		CVA LF (38 cases) HEMISP		CVA BRA (17 cases) STEM	
#	Day	#	Day	#	Day
5 -	1	4 -	1	2 -	1
9 -	2	16 -	2	8 -	2
2 -	3	7 -	3	3 -	3
8 -	4	2 -	4	1 -	4
3 -	5	6 -	5	1 -	5
1 -	6	1 -	7	1 -	7
2 -	7	1 -	8	1 -	11
1 -	9	1 -	12		
2 -	11				

$\Sigma x_{1j} = 127$ $\qquad \Sigma x_{2j} = 122$ $\qquad \Sigma x_{3j} = 54$

$\Sigma x_{1j}^2 = 719$ $\qquad \Sigma x_{2_j}^2 = 570$ $\qquad \Sigma x_{3j}^2 = 272$

$\bar{x}_1 = 3.84848$ $\qquad \bar{x}_2 = 3.21053$ $\qquad \bar{x}_3 = 3.17647$

$C = 303^2/88$ or 1043.2841

$\Sigma\Sigma x_{ij}^2 = 1561$

$SST = 1561 - 1043.2841$ or 517.7159

$SSB = 127/^2/33 + 122^2/38 + 54^2/17 - C$ or 8.6871

$SSE = 517.7159 - 8.6871$ or 509.0288

$F = \frac{8.6871/2}{509.0288/85}$ or $.7252 < 3.12$ at .05 level i.e. means not significantly different.

Admission Class: On the basis of the neurologic examination and scoring detailed in Appendix II performed upon arrival to the Stroke Unit, each patient was placed into one of five Classes describing increasingly severe deficits. These classes are defined on page 9.

The spectrum of impairments at presentation are listed in Table I and VIa. Most patients presented with an intermediate degree of impairment with fewer numbers at the extremes. This distribution of deficit types is not different from that of the 208 patients whose strokes did not progress in the Unit as calculated in Table I by the chi-square test.

TABLE VIa

ADMISSION CLASS

I (7 cases)	II (26 cases)	III (36 cases)	IV (25 cases)	V (11 cases)
# DAY	# DAY	# DAY	# DAY	# DAY
1 - 3	4 - 1	4 - 1	3 - 1	2 - 1
2 - 5	10 - 2	12 - 2	9 - 2	6 - 2
1 - 7	3 - 3	6 - 3	5 - 3	1 - 3
2 - 10	3 - 4	6 - 4	3 - 4	1 - 7
1 - 11	3 - 5	3 - 5	3 - 5	1 - 11
	1 - 6	1 - 6	1 - 7	
	1 - 7	1 - 8	1 - 12	
	1 - 8	1 - 9		
		2 - 11		
$\Sigma x_{1j} = 51$	$\Sigma x_{2j} = 81$	$\Sigma x_{3j} = 130$	$\Sigma x_{4j} = 82$	$\Sigma x_{5j} = 35$
$\Sigma x^2_{1j} = 429$	$\Sigma x^2_{2j} = 343$	$\Sigma x^2_{3j} = 700$	$\Sigma x^2_{4j} = 400$	$\Sigma x^2_{5j} = 205$
$\bar{x}_1 = 7.2857$	$\bar{x}_2 = 3.1154$	$\bar{x}_3 = 3.6111$	$\bar{x}_4 = 3.2800$	$\bar{x}_5 = 3.1818$

$C = 379^2/105$ or 1368.0095

$\Sigma\Sigma x^2_{ij} = 2077$

$SST = 2077 - 1368.0095$ or 708.9905

$SSB = 51^2/7 + 82^2/26 + 130^2/36 + 82^2/25 + 35^2/11 - C$ or 105.6761

$SSE = 708.9905 - 105.6761$ or 603.3144

$F = \frac{105.6761/4}{603.3144/100}$ or $4.3790 > 2.71$ at .05 level ie.e means are significantly different

In the analysis of the mean day of progression by Admission Class group, the seven patients with a history of TIA's only; that is, Class I at admission, show a mean of 7.29 days, as contrasted to the means of 3.12, 3.61, 3.28, 3.18 days for Admission Class II through V,

respectively. Table VIb evaluates these latter four classes; no statistical difference is found as to the subsequent mean day of progression among patients presenting with permanent deficits, no matter the initial degree of disability, whereas those patients admitted with TIA's have a significantly later occurrence of progression.

TABLE VIb

ADMISSION CLASS WITHOUT CLASS I

$C = 328^2/98$ or 1097.7959

$\Sigma\Sigma x_{ij}^2 = 1648$

$SST = 1648 - 1097.7959$ or 550.2041

$SSB = 81^2/26 + 132^2/36 + 82^2/25 + 35^2/11 - C$ or 4.3183

$SSE = 550.2241 - 4.3183$ or 545.8858

$F = \frac{4.3183/3}{545.8858/94}$ or $.2479 < 2.71$ at .05 level i.e. means not significantly different

Length of Hospitalization: 104 of the 105 cases of progressing stroke ultimately were discharged. Eight were discharged by hospital day ten; twenty-nine were discharged eleven to nineteen days after admission. Thirty-three were discharged between twenty and twenty-nine days later and thirty-four cases were sent home one month to ninety-nine days after initial admission to the Unit. Table VII illustrates that the day on which progression occurred had no bearing on the day on which the patient was discharged.

TABLE VII

LENGTH OF HOSPITALIZATION

1-10 DAYS (8 cases)		11-19 DAYS (29 cases)		20-29 DAYS (33 cases)		30-99 DAYS (34 cases)	
#	Day	#	Day	#	Day	#	Day
2	1	5	1	4	1	2	1
4	2	9	2	14	2	9	2
2	3	3	3	4	3	7	3
		2	4	3	4	7	4
		6	5	4	5	1	5
		2	6	2	7	2	7
		1	9	1	10	2	8
		1	10	1	11	3	11
						1	12

$\Sigma x_{1j} = 16$	$\Sigma x_{2j} = 101$	$\Sigma x_{3j} = 111$	$\Sigma x_{4j} = 149$
$\Sigma x_{1j}^2 = 36$	$\Sigma x_{2j}^2 = 503$	$\Sigma x_{3j}^2 = 563$	$\Sigma x_{4j}^2 = 971$
$\bar{x}_1 = 2.0000$	$\bar{x}_2 = 3.4828$	$\bar{x}_3 = 3.3636$	$\bar{x}_4 = 4.3824$

$C = 377^2/104$ or 1366.6250

$\Sigma\Sigma x_{ij}^2 = 2073$

SST = 2073 - 1366.6250 or 706.3750

SSB = $16^2/8 + 101^2/29 + 111^2/33 + 149^2/34 - C$ or 43.4678

SSE = 706.3750 - 43.4678 or 662.9072

$F = \frac{43.4678/3}{662.9072/100}$ or 2.1857 < 2.71 at .05 level i.e. means not significantly different

Seizure activity: Patients were carefully watched and monitored with E E G for seizure activity. Only eight of the 105 cases of stroke-in-progress exhibited seizures in the acute period. These few patients had an earlier mean day of progression at 2.25 days compared to the mean of 3.72 days for the remaining 97 cases where no seizure activity was detected. As calculated in Table VIII the means are not statistically different, however.

TABLE VIII

SEIZURE ACTIVITY

NO (97 cases)	YES (8 cases)
# Day	# Day
9 - 1	4 - 1
36 - 2	1 - 2
15 - 3	1 - 3
11 - 4	1 - 4
10 - 5	1 - 5
2 - 6	
4 - 7	
2 - 8	
1 - 9	
2 - 10	
4 - 11	
1 - 12	
$\Sigma x_{1j} = 361$	$\Sigma x_{2j} = 18$
$\Sigma x^2_{1j} = 2019$	$\Sigma x^2_{2j} = 58$
$\bar{x}_1 = 3.7216$	$\bar{x}_2 = 2.25$

$C = 379^2/105$ or 1368.0095

$\Sigma\Sigma x^2_{ij} = 2077$

$SST = 2077 - 1368.0095$ or 708.9905

$SSB = 361^2/97 + 18^2/8 - C$ or 16.0060

$SSE = 708.9905 - 16.0060$ or 692.9845

$F = \frac{16.0060/1}{692.9845/103}$ Or $2.5517 < 3.94$ at .05 level i.e. means not significantly different

Cardiac Disease: Patients were regarded as having evidence of cardiac disease if they provided a positive history of angina, infarction, failure, use of cardiac medication, prosthetic value or pacemaker placement. Also included were patients with pathologic murmurs, cardiomegaly or failure on chest x-ray, or an abnormal E K G Table IX

provides the days on which progression was noted in the fifty-four patients with at least one abnormal cardiac finding compared to the fifty-one patients without evidence of cardiac disease. The mean days of progression were 3.76 and 3.45 days, which are not statistically different.

TABLE IX

EVIDENCE OF CARDIAC DISEASE

NO (51 cases) #	Day	YES (54 cases) #	Day
3	1	10	1
21	2	16	2
13	3	3	3
3	4	9	4
5	5	6	5
1	6	1	6
1	7	3	7
1	8	1	8
2	11	1	9
1	12	2	10
		2	11

$\Sigma x_{1j} = 176$ $\qquad$ $\Sigma x_{2j} = 203$

$\Sigma x_{1j}^2 = 912$ $\qquad$ $\Sigma x_{2j}^2 = 1165$

$\bar{x}_1 = 3.4510$ $\qquad$ $\bar{x}_2 = 3.7593$

$C = 379^2/105$ or 1368.0095

$\Sigma\Sigma x_{ij}^2 = 2077$

$SST = 2077 - 1368.0095$ or 708.9905

$SSB = 176^2/51 + 203^2/54 - C$ or 2.4926

$SSE = 708.9905 - 2.4926$ or 706.4979

$F = \frac{2.4926/1}{706.4979/103}$ or $.3634 < 3.94$ at .05 level i.e. means not significantly different

Among these fifty-four patients with cardiac disease, forty-eight exhibited dysrhythmias while monitored in the Stroke Unit, including brady-and tachy-dysrhythmias. Their mean day of progression was 3.33

days as indicated in Table X. Again, this is not significantly different from the mean day of 3.84 days for those patients remaining in normal sinus rhythm.

TABLE X

CARDIAC DYSRHYTHMIAS

NO (57 cases) #	Day	YES (48 cases) #	Day
5	1	8	1
22	2	15	2
8	3	8	3
4	5	4	4
1	6	7	5
1	7	1	6
2	8	3	7
2	10	1	9
3	11	1	11
1	12		

$\Sigma x_{1j} = 219$ $\Sigma x_{2j} = 160$

$\Sigma x_{1j}^2 = 1313$ $\Sigma x_{2j}^2 = 764$

$\bar{x}_1 = 3.8421$ $\bar{x}_2 = 3.3333$

$C - 379^2/105$ or 1368.0095

$\Sigma\Sigma x_{ij}^2 = 2077$

$SST = 2077 - 1368.0095$ or 708.9905

$SSB = 219^2/57 + 160^2/48 - C$ or 6.7449

$SSE = 708.9905 - 6.7449$ or 702.2456

$F = \frac{6.7449/1}{702.2456/103}$ or $.9893 < 3.94$ at .05 level i.e. means not significantly different

Blood Pressure: The effects of systolic blood pressure on the time course of stroke progression was evaluated in several manners. Firstly, an attempt was made to correlate the mean day of stroke progression with admission systolic and diastolic readings. For the statistical analysis

systolic blood pressure effects of 104 patients were classified into three ranges with one patient excluded because of an erroneous recording. These arbitrary ranges were labeled "normal" for admission systolic values of 110-129 mmHg; "high normal" for systolic readings of 130-149 mmHg; and "high" for systolic readings greater than 150 mmHg. Table XI indicates that of the 104 patients so classified wholly eighty-one had admission systolic blood pressures greater than 150mmHg. In comparing the mean days of extension of deficit among the three systolic blood pressure groups, the "high" systolic blood pressure group extended earlier at 3.43 days compared to 4.13 days for the eight patients with "normal" systolic blood pressures at admission and 4.27 days for the fifteen patients admitted with systolic readings in the 130-149 mmHg range. The difference among the groups is noted to be without statistical significance.

TABLE XI

SYSTOLIC BLOOD PRESSURE

"NORMAL" (8 cases)		"HI-NORM" (15 cases)		"HIGH" (81 cases)	
#	Day	#	Day	#	Day
4	2	7	2	13	1
1	4	2	3	26	2
2	5	1	4	14	3
1	11	2	5	9	4
		1	8	7	5
		2	11	2	6
				4	7
				1	8
				1	9
				2	10
				1	11
				1	12

$\Sigma x_{1j} = 33$ $\quad \Sigma x_{2j} = 64$ $\quad \Sigma x_{3j} = 378$

$\Sigma x^2_{1j} = 203$ $\quad \Sigma x^2_{2j} = 418$ $\quad \Sigma x^2_{xj} = 1440$

$\bar{x}_1 = 4.1250$ $\quad \bar{x}_2 = 4.2667$ $\quad \bar{x}_3 = 3.4321$

$C = 375^2/104$ or 1352.1635

$\Sigma\Sigma x^2_{ij} = 2061$

$SST = 2061 - 1352.1635$ or 708.8365

$SSB = 33^2/8 + 64^2/15 + 278^2/81 - C$ or 11.1517

$SSE = 708.8365 - 11.1517$ or 697.6848

$F = \dfrac{11.1517/2}{697.6848/101}$ or $.8072 < 3.10$ at .05 level i.e. means not significantly different

In Table XII similar procedures were applied to the analysis of the effect of diastolic blood pressure on the time of progression. Ninety-nine of the 105 patients had a clear record of their admission diastolic blood pressure. They were classified as "normal" for admission diastolic recordings in the range of 70-85 mmHg; "high normal" for recordings in the 85-100 mmHg range; and "high" for admission diastolics greater than 100 mmHg. In Table XII again the largest group of patients (39)

were in the "high" range. This group has an earlier mean day of extension at 3.03 days compared to 4.00 and 4.5 days for the "high normal" and "normal" groups, respectively. However, there is no statistical difference among these three means.

TABLE XII

DIASTOLIC BLOOD PRESSURE

"NORMAL" (26 cases)		"HI-NORM" (34 cases)		"HIGH" (39 cases)	
#	Day	#	Day	#	Day
3	1	4	1	6	1
11	2	9	2	13	2
2	3	6	3	8	3
1	4	3	4	7	4
3	5	4	5	3	5
1	6	1	6	1	7
1	8	3	7	1	12
4	11	1	8		
		1	9		
		2	10		
$\Sigma x_{1j} = 108$		$\Sigma x_{2j} = 136$		$\Sigma x_{3j} = 118$	
$\Sigma x_{1j}^2 = 740$		$\Sigma x_{2j}^2 = 770$		$\Sigma x_{3j}^2 = 510$	
$\bar{x}_1 = 4.1538$		$\bar{x}_2 = 4.0000$		$\bar{x}_3 = 3.0256$	

$C = 362^2/99$ or 1323.6768

$\Sigma\Sigma x_{ij}^2 = 2020$

$SST = 2020 - 1323.6768$ or 696.3232

$SSB = 108^2/26 + 136^2/34 + 118^2/39 - C$ or 25.9642

$SSE = 696.3232 - 25.9642$ or 670.3590

$F = \dfrac{25.9642/2}{670.3590/96}$ or $1.8591 < 3.10$ at .05 level i.e. means not significantly different

The effect of systemic blood pressure in the acute setting was examined in another manner. Those patients whose record showed a rise in mean blood pressure of greater than 10 mmHG during the week of extension

were grouped for statistical analysis separately from patients who did not have such episodic hypertension. Table XIIIa lists the sixteen patients exhibiting this blood pressure elevation phenomenon along with their respective days of extension. Their mean day of extension was 3.75 days, whereas the eighty-nine patients without hypertensive episodes during the first week of stroke showed a mean day of 3.58 days, which is not statistically different.

TABLE XIIIa

BLOOD PRESSURE ELEVATION (>10mmHg mean bp)

NO (89 cases)		YES (16 cases)	
#	Day	#	Day
10 -	1	3 -	1
33 -	2	4 -	2
13 -	2	3 -	3
11 -	4	1 -	4
9 -	5	2 -	5
1 -	6	1 -	6
4 -	7	1 -	8
1 -	8	1 -	12
1 -	9		
2 -	10		
4 -	11		

$\Sigma x_{1j} = 319$ $\Sigma x_{2j} = 60$

$\Sigma x_{1j}^2 = 1721$ $\Sigma x_{2j}^2 = 356$

$\bar{x}_1 = 3.5843$ $\bar{x}_2 = 3.7500$

$C = 379^2/105$ or 1368.0095

$\Sigma\Sigma x_{ij}^2 = 2077$

$SST = 2077 - 1368.0095$ or 708.9905

$SSB = 319^2/89 + 60^2/16 - C$ or $.3725$

$SSE = 708.9905 - .3725$ or 708.6180

$F = \dfrac{.3725/1}{708.6180/103}$ or $.05414 < 3.94$ at .05 level
i.e. means not significantly different

Table XIIIb examines the frequency of blood pressure elevations of greater than 10mmHg during the week of the stroke in progressing stroke compared to the population of 208 patients in the Unit who did not progress. By chi-square analysis, this phenomenon is shown to in no way characterize the population with progression from the stable acute stroke group.

TABLE XIIIb

BLOOD PRESSURE ELEVATION (progressing versus non-progressing group)

	NO	YES	TOTALS
PID	89 (90.91)	16 (14.09)	105
NP	182 (180.09)	26 (27.91)	208
TOTALS	271	42	313

$X^2 = .450 < 3.841$ with 1 d.f. at .05 level i.e. distributions <u>not</u> significantly different

An attempt was made to determine the effects of chronic hypertension on the temporal profile of stroke evolution. A positive past history of hypertension, whether or not under treatment was obtained from approximately one-half of the patients exhibiting stroke-in-progress. The days on which progression occurred in this group of fifty-three as well as the fifty-two patients providing normal blood pressure histories are listed in Table XIVa. Those with a past history of hypertension had progression noted on a mean day of 3.076. The patients without such a history progressed with a mean day 4.15 days which is significantly later.

TABLE XIVa

HISTORY OF HYPERTENSION

No Hypertension (52 cases)		Hypertension (53 cases)	
#	Day	#	Day
5	1	8	1
19	2	18	2
5	3	11	3
3	4	9	4
9	5	2	5
1	6	1	6
2	7	2	7
2	8	1	9
2	10	1	11
3	11		
1	12		

$\Sigma x_{1j} = 216 \quad \Sigma x_{1j}^2 = 1368$ $\qquad$ $\Sigma x_{2j} = 163 \quad \Sigma\, x_{2j}^2 = 709$

$\bar{x}_1 = 4.1538$ $\qquad$ $\bar{x}_2 = 3.0755$

$C = 379^2/105$ or 1368.0095

$\Sigma\Sigma x_{ij}^2 = 2077$

$SST = 2077 - 1368.0095$ or 708.9905

$SSB = 216^2/52 + 163^2/53 - C$ or 30.5232

$SSE = 708.9905 - 30.5232$ or 678.4673

$$F = \frac{30.5232/1}{678.5673/103} \quad \text{or } 4.6338 > 3.94 \text{ at .05 level}$$

i.e. means are significantly different

It was observed that the group of patients without a history of hypertension included six of the seven cases presenting in Admission Class I; that is, patients with acute histories of transient focal neurologic deficits of less than twelve hours duration at the time of admission. As previously noted in Tables VIa and VIb, this group had already been identified as progressing later than the other four classes of patients presenting with permanent deficits. Therefore, the patients with and without a history of hypertension were compared for mean day of exten-

sion after excluding those patients presenting with TIA's only. Table XIVb shows that these fifty-two with a history of hypertension had a mean day of progression of 3.08 days compared to a mean of 3.65 days for the group with a negative blood pressure history. The difference between these means is without statistical significance.

TABLE XIVb

HISTORY OF HYPERTENSION
(Without Admission Class I)

No Hypertension (46 cases)		Hypertension (52 cases)	
#	Day	#	Day
5	1	8	1
19	2	18	2
5	3	10	3
3	4	9	4
7	5	2	5
1	6	1	6
1	7	2	7
2	8	1	9
2	11	1	11
1	12		

$\Sigma x_{1j} = 168$ $\qquad$ $\Sigma x_{2j} = 160$

$\Sigma x_{1j}^2 = 948$ $\qquad$ $\Sigma x_{2j}^2 = 700$

$\bar{x}_1 = 3.6522$ $\qquad$ $\bar{x}_2 = 3.0769$

$C = 328^2/98$ or 1097.7959

$\Sigma\Sigma x_{ij}^2 = 1648$

$SST = 1648 - 1097.7959$ or 550.2041

$SSB = 168^2/46 + 160^2/52 - C$ or 8.0770

$SSE = 550.2041 - 8.0770$ or 542.1271

$$F = \frac{8.0770/1}{542.1271/96} \text{ or } 1.4303 < 3.95 \text{ at .05 level}$$

i.e. means not significantly different

Finally, the effects of elevated blood pressure on the mean day of stroke progression was examined by separately evaluating the mean day of progression of the few patients whose acute hypertension required treatment in the judgment of the attending physician. Table XV notes that the small group of eleven treated patients showed a mean of 2.18 days, whereas the ninety-one not receiving anti-hypertensive medication showed a mean of 3.78 days. These means are not statistically different at the .05 level; the difference is significant at the .10 level.

TABLE XV

ANTI-HYPERTENSIVE TREATMENT

YES (11 cases) #	Day	NO (94 cases) #	Day
2	1	11	1
5	2	32	2
4	3	12	3
		12	4
		11	5
		2	6
		4	7
		2	8
		1	9
		2	10
		4	11
		1	12

$\Sigma x_{1j} = 24$ $\Sigma x_{2j} = 355$

$\Sigma x_{1j}^2 = 58$ $\Sigma x_{2j}^2 = 2019$

$\bar{x}_1 = 2.1818$ $\bar{x}_2 = 3.7766$

$C = 379^2/105$ or 1368.0095

$\Sigma\Sigma x_{ij}^2 = 2077$

$SST - 2077 - 1368.0095$ or 708.9905

$SSB = 24^2/11 + 355^2/94 - C$ or 25.0456

$SSE = 708.9905 - 25.0456$ or 683.9449

$F = \dfrac{25.0456/1}{683.944/103}$ or $3.7718 < 3.94$ at .05 level
$3.7718 > 2.76$ at .10 level

i.e. means <u>not</u> significantly different at .05 level but significantly different at .10 level.

History of Diabetes: Patients were selected out of the study who provided a seemingly reliable history of longstanding treated or untreated diabetes mellitus. In twenty-six of the 105 cases of progressing stroke, a positive history was obtained. This group had a mean day of progression of 3.96 days. The seventy-nine patients not providing a past medical history of diabetes had a mean day of progression of 3.49 days, which is not statistically different as calculated in Table XVI.

TABLE XVI

HISTORY OF DIABETES

NO (79 cases)		YES (26 cases)	
#	Day	#	Day
9	1	4	1
31	2	6	2
13	3	3	3
5	4	7	4
10	5	1	5
1	6	1	6
3	7	1	7
2	8	1	10
1	9	2	11
1	10		
2	11		
1	12		

$\Sigma x_{1j} = 276$ $\Sigma x_{2j} = 103$

$\Sigma x_{1j}^2 = 1458$ $\Sigma x_{2j}^2 = 619$

$\bar{x}_1 = 3.4937$ $\bar{x}_2 = 3.9615$

$C - 379^2/102$ or 1368.0095

$\Sigma\Sigma x_{ij}^2 = 2077$

$SST = 2077 - 1368.0095$ or 708.9905

$SSB = 276^2/79 + 103^2/26 - C$ or 4.2822

$SSE = 708.9905 - 4.2822$ or 704.7083

$F = \dfrac{4.2822/1}{704.7083/103}$ or $.6259 < 3.94$ at .05 level i.e., means not significantly different

Previous Strokes: Thirty-three of the 105 patients gave a past medical history of stroke. This group had a mean day of 4.26 days compared to 3.48 days for the seventy-two patients who were admitted with their first cerebrovascular attack.

Patients showing stroke-in-progress showed the same time course of evolution of their deficit regardless of their past stroke history, as outlined in Table XVII.

TABLE XVII

PREVIOUS STROKES

YES (33 cases)

#	Day
5	1
7	2
5	3
3	4
7	5
1	6
2	8
1	10
2	11

NO (72 cases)

#	Day
8	1
30	2
11	3
9	4
4	5
1	6
4	7
1	9
1	10
2	11
1	12

$\Sigma x_{1j} = 135$ $\qquad$ $\Sigma x_{2j} = 244$

$\Sigma x^2_{1j} = 807$ $\qquad$ $\Sigma x^2_{2j} = 1270$

$\bar{x}_1 = 4.0909$ $\qquad$ $\bar{x}_2 = 3.3889$

$C = 379^2/105$ or 1368.0095

$\Sigma\Sigma x^2_{ij} = 2077$

$SST = 2077 - 1368.0095$ or 708.9905

$SSB = 135^2/33 + 244^2/72 - C$ or 11.1521

$SSE = 708.9905 - 11.1521$ or 697.8384

$F = \frac{11.1521/1}{697.8384/103}$ or $1.6460 < 3.94$ at .05 level

i.e. means not significantly different

CHAPTER 8

DISCUSSION

The patients entered into this study came to the West Haven Veteran's Administration Hospital Stroke Study Unit intensive care facility from the New Haven community hospitals, as well as through the V A Emergency Room, thus comprising an apparently adequate demographic representation of an acute ischemic stroke population in the general community: For the total ischemic stroke population of 313 cases, the mean age was 66.48 years, with a standard deviation of 11.70 years; the sub-group that showed progression was statistically indistinguishable having a mean age of 67.2 years, with a standard deviation of 11.39 years, as noted on page 13. The age characterization of this ischemic stroke population is in very close agreement with other studies.(1, 33, 39, 40, 54, 55)

The age compositions of the two sexes were evaluated separately. On page 13 the females are found to have a mean age of 70.60 years which is shown to be significantly older than the mean of 64.59 years for the males. Again, this is in agreement with other studies.(39,42,55) Also, perhaps typifying the ischemic stroke population, males predominated the number of admissions, which has also been remarked upon in the literature.(1,10,19,24,33,40,42,44,55,58) Others have de-emphasized the role of sex as a major risk factor.(59,60)

In the population studied in the Unit, the patients presented with a spectrum of severities of deficit. The largest number of patients presented with intermediate degrees of impairment. Table I shows that the patients subsequently showing progression of their deficit and those remaining stable were initially admitted with the same spectrum of stroke

severities; degree of impairment at admission is not predictive of possible progression.

The most illuminating observation of the study is revealed in Table II: 37 of the 105 cases of stroke-in-progress exhibited progression during the second day in the Unit. This quantitatively substantiates the "day or two" time course characterizing progression alluded to by many of the authors discussed in Appendix I. In the rest of the tables the temporal profile of the progressing stroke population is examined with respect to factors that might influence stroke evolution. As these factors are individually discussed in the following pages, it becomes evident that, by and large, the evolving stroke process is truly characterized by the time course described in Table II. Furthermore, this process is characterized by the independence of this time course from the hypothesized control factors.

First, the influences of sex and age on the time course of evolution were evaluated (Tables III and IV); neither seems to affect the time course for the population.

As already mentioned, the severity of deficit at admission was not predictive of subsequent progression. The degree of deficit also does not influence the rate of progression; (Tables VIa-b). This observation is with the noted exception of those patients admitted with a history of transient focal neurologic deficits of less than 12 hours' duration; that is, TIA cases. They are shown to exhibit progression later on (a mean of over a week) in their hospitalization. The possible pathophysiological and treatment implications of this finding are discussed in the following pages on anticoagulation therapy trials from the literature.

Others have noted that the length of stay in the hospital stroke

patients require is often correlated with the severity of the acute event.(61) In another attempt to indirectly evaluate the influence of the severity of the insult on the temporal profile of progressing stroke, patients were grouped according to the number of days of hospitalization they ultimately required (Table VII). Again, by this indirect evaluation, stroke severity did not control the time course of evolution.

SITE: Approximately one fifth of the localizable infarcts were in the brain stem. The remainder were divided equally between the hemispheres. This distribution is similar to that found for ischemic strokes in general.(30,33) In commenting specifically on the temporal profile of progressing stroke, Millikan states: "If the site of the lesion is in the carotid system, 18 to 24 hours without progression is ordinarily sufficient time to mean that further progression is unlikely and that the patient's temporal profile status should no longer be categorized as 'progressing stroke.' If the lesion is in brain supplied by the vertebrobasilar system, a longer period of time (up to 72 hours) should probably elapse before the patient is removed from the progressing stroke category and is designed as a 'completed stroke,' since there is a tendency for periods of progression to be separated by many hours when the impaired circulation is in the vertebrobasilar system."(62)

This study did not reveal differences in time course between the hemispheres and brain stem. In lesions of either the posterior or anterior circulations, the greatest number of patients progressed on Day Two. With the neurological examination system outlined in Appendix II, including serial testing of cortical as well as cranial nerve function, late progression, after 48 hours, was detected as commonly in the hemispheres as the brain stem.

SEIZURES: The presence of seizures or post-ictal states at the time of admission confused the neurological evaluation of the severity of stroke deficit; these records were therefore excluded from the statistical analysis. These case selection criteria weaken any statements as to the frequency and role of seizures in progressing stroke. Table VIII shows that 97 of the 105 cases of evolving stroke in the study did not evidence seizure activity clinically or on electroencephalographic monitoring. In this great majority, seizures cannot be implicated as responsible for, or a product of, progression. In embolic and especially thrombotic strokes in general, seizure activity has been noted to occur relatively infrequently.(1,53) For the few patients having seizures in the acute interval, the mean time course was earlier at 2.25 days, but the difference was without statistical significance.

CARDIOVASCULAR DISEASE: The results of this study imply that the evolving stroke process is not directly dependent upon a changing cardiovascular status of the patient. The group of patients with evidence of cardiac disease (Table IX), and specifically the sub-group displaying cardiac dysrhythmias (Table X), showed no differences in the temporal profile of the evolving stroke from the group without detected cardiac abnormalities.

Several studies have shown that cardiac dysrhythmias are commonly observed in the context of cerebral insufficiency.(63-66) These observations will surely become commonplace if stroke intensive care unit monitoring becomes more popular.(67) However, dysrhythmic episodes have not correlated well with the occurrence of the neurological events.(66,68,69)

A simple explanation for the observation of frequent cardiac abnormalities in the acute stroke population is that atherosclerosis affects

the vasculature of many organ systems. There are numerous reports of the high concurrenceof cerebral and myocardial ischemic disease.(19,38,53,60,70-73)

A fascinating alternative explanation for the apparent lack of dependence of the progressing stroke time course on the patients' acute cardiac abnormalities is that the cerebral damage causes the cardiac abnormalities. This might occur through a variety of mechanisms or combinations: 1) the brain infarction might cause the release of arrhythmogenic substances; (73,74) 2) the infarction might cause distant effects upon the central autonomic control center; (75-80) or 3) the central event might precipitate an actual myocardial infarction(81-83) or contribute to the widening of the area of myocardial ischemia and infarction.(84) Each hypothesis suggests different directions for experimental and clinical evaluation and possible intervention. More careful study might reveal new insight into the treatment of both cerebral and myocardial ischemic disease.

The fact that the group with cardiac dysrhythmias progressed with the same chronology as did those without dysrhythmias argues against one suggested mechanism for stroke progression, namely, that transient systemic hypotensive episodes are responsible for progression.(5,85) This theory is suggested by the finding that cerebral circulation is decreased evanescently during cardiac dysrhythmias.(86,87) This has led many authors to implicate systemic hypotension as a common precipitating factor for focal cerebral ischemic attacks.(42,88-93) Others, however, have argued that episodic hypotension rarely can be implicated as the precipitating event in focal cerebral ischemic events.(20,94-99)

Whatever role systemic hypotension plays in initiating the stroke process, this study of patients with progressing strokes and concomitant

dysrhythmias suggests that once the stroke process has begun, it is independent to some degree of the effects of blood pressure changes. Consistent with this hypothesis, the few patients in this study treated with anti-hypertensive medication (Table XV) showed neither an accelerated nor a prolonged time course of evolution. Others have safely employed hypotensive agents in the acute stroke setting.(100)

The lack of correlation between the time course of the evolving stroke and blood pressure fluctuations is further suggested by the observation that among the patients who exhibited acute elevation in mean blood pressure of greater than 10mmHG (Table XIIa) there was no noticeable difference in the temporal profile of evolution. Table XIIIb suggests that elevation of blood pressure is as common in acute stroke whether stable or under progression.

Hayakawa and Waltz studied the pathological changes at 48 hours correlated with changes in pulse rate (P R) and mean aorta blood pressure (MABP) in 12 tranquilized cats with MCA surgical occlusion and one control animal.(101) They concluded that "fluctuation of M A B P and P R did not appear to affect the outcome of the ischemic process or the extent of the resulting infarcts." No specific comment was made as to the time course of evolution of the infarcts. They add, however, that "the moderate increases of M A B P that occurred after M C A occlusion in two cats that had small infarcts suggests a possible protective effect of moderate hypertension." Clinically, artificial elevation of blood pressure has been attempted as a therapeutic intervention. The efficacy of pressors to reverse the symptoms of cerebral vascular insufficiency has been reported.(102) In primate models, however, artificial blood pressure augmentation caused systemic complications of the procedure, namely CHF, that negated any possible positive effects.(103)

HYPERTENSION: As with vascular disease of other organ systems, the presence of hypertension has been identified as a substantial but treatable risk factor for the development of a cerebral vascular accident. Hypertension has been judged to be present according to different accepted upper limits of normal systolic and/or diastolic readings. The blood pressure determinations have been made on single or multiple occasions in the acute stroke setting or on routine examination. Although the definitions of the hypertensive population have differed, there is widespread agreement that hypertension predisposes to stroke.(40,53,55,58,60,72,104) Admittedly, the stroke population has an older median age than the general population and so has a higher incidence of hypertension.(59) However, it has been found since the time that chronic hypertension could be effectively controlled, its treatment has reduced the incidence of both hemorrhagic and ischemic strokes.(105,106)

The influence of hypertension on the early prognosis of a stroke is less clear. Balow, et al. reviewed 100 cases of thromboembolic stroke;(33) 48 had a history of elevated blood pressure and 17 additional patients had admission diastolic readings over 90 mm Hg. Among these 65, 42% died or failed to improve one month after their stroke. However, little difference was noted among the 35 normotensive individuals; 46% of them had died or failed to improve over the same follow-up interval. Hurwitz, et al., likewise could find no increased early morbidity and mortality among the 23 patients with carotid occlusive disease and blood pressures of greater than 140/90 mm Hg compared to the 31 normotensive patients with carotid disease.(19) Carter notes in his study of 612 cases of cerebral infarction that, contrary to his own expectations, he found no difference in the death rate at one month between the 392 patients with diastolic

pressures over 110 mm Hg or systolic pressures over 200 mm Hg than the 220 patients without such hypertension.(30) He discusses hypertension as a poor prognostic factor only when longterm survival is considered. This opinion is supported by others.(24,44,57) Fujishima, et al, attempted to identify the effects of hypertension on stroke recovery in patients with cerebrovascular occlusive disease.(107) Eleven of 16 hypertensive patients were not improved a month after their strokes, whereas only one of nine normotensive patients had not improved. Rankin found only a slightly increased early mortality rate for stroke patients with hypertension, which was associated with concomitant congestive heart failure.(10) In a longitudinal study of 3983 men Rankin found that elevated systolic blood pressure, and its upward trend over five years, were associated with increased mortality 30 days after stroke.(108)

Adams showed that both systolic and diastolic blood pressures are markedly elevated above baseline in the immediate several weeks after the stroke insult.(109) This clinical observation was noted years earlier by Gilbert and de Takats.(2) Low-Beer and Phear, however, reported that blood pressures of stroke victims on admission are reliable for baseline assessment.(110) Allowing for this disagreement, the hypertensive population for this study was defined by history of elevated blood pressure and by elevated systolic or diastolic blood pressures on admission. (Tables XI, XII, and XIV).

78.8% of the 105 cases of progressing stroke had systolic blood pressures over 150 mm Hg on admission. Among the general stroke population Perkin reported that a similar 73% of patients had over 150 mm Hg.(111) Aring and Merritt found that among patients with thrombotic strokes, 70% had systolic blood pressures over 160 mm Hg and 52% had diastolic

readings over 100 mm Hg.(1) In this study diastolic readings above 100 mm Hg at admission were found in 39.7% of the cases of progressing stroke. Also similar to other studies of ischemic strokes in general was the finding that 50.4% of the patients with progressing stroke provided a history of hypertension. Mohr, et al. report that 55% of the patients with large artery thrombotic strokes and 40% of the patients with embolic strokes provided such a history.(53)

In evaluating the role of blood pressure on regulating the time course of stroke progression, Tables XI-XIII and XV show that none of the measures of hypertension in the acute setting is predictive of an aberrant time course of progression. Only the attempt to access chronic hypertension by past history (Table XIVa) was shown to prognose a group with an accelerated mean time course. This finding would fit well with the experimental and autopsy studies showing that hypertension accelerates angiopathy.(112-114) This would argue for a vascular control mechanism over the time course of progression. However, closer review of the hypertensive population with progression shows that among the 52 cases, there was only one patient presenting in Admission Class I, whereas the other six in this Class were included among those providing no history of hypertension. The delayed time course of these few patients was shown to provide an explanation for the apparently accelerated course of the hypertensives (Table XIVb). Clearly, for the large numbers of patients presenting with permanent cerebral damage, past hypertension and its possible effects are seemingly overshadowed by other presumed control factors. It is difficult to explain why most of the patients presenting with TIA's were among those with no history of hypertension. Perhaps it is mere chance alone. Curiously, Lindgren has stated that patients with a history of hypertension have transient attacks more frequently than do normotensives.(12)

DIABETES: As with the patients with a history of hypertension, reports have shown an association between a history of diabetes mellitus and cerebrovascular disease.(59,115-117) This association is even more impressive if patients with thromboembolic strokes are evaluated.(53,55, (72,118) In fact estimations of the co-incidence of these two diseases may be low, as glucose tolerance testing reveals many cases of covert diabetes in the stroke population. Gertler, et al found as many as 76% of a population with ischemic thrombotic cerebrovascular disease have abnormal oral GTT's compared to 22% of the healthy control patients without a family history of diabetes, 32% of the healthy controls with a positive family history, and only 39% of the patients with ischemic heart disease.(119)

Longstanding diabetes may accelerate the processes leading to an ischemic stroke. Frithz and Werner note that diabetes is common in the stroke population under age 50.(120) Smooth muscle cell culture experiments suggest a mechanism. Ledet, et al. found that diabetes serum contains an arterial smooth muscle cell growth factor(s) that they suggest leads to angiopathy.(121) In post-mortem study the atherosclerotic processes are more advanced in diabetics.(122,123) James implies that possibly diabetics are stroke-prone as a result of the adverse effects of the disease on the autonomic nervous system regulation of vascular resistance.(124) As West discusses at length, it has, of course, been difficult to directly relate diabetes and stroke; the high incidence of hypertension among diabetics may explain much of the association.(154)

In the present study we attempted to evaluate the possiblity that the diabetic might show a differing time course of stroke-in-progress; this would indirectly suggest that a vascular mechanism is partly responsible for the temporal profile. Patients were evaluated for the presence of

diabetes by history, since it was felt that the phenomenon of reactive hyperglyceremia in the acute stroke setting(1,125) and the in-hospital management of blood sugars made laboratory values of reduced significance.

The results of the study indicated no difference in the time course of evolution in the diabetics and non-diabetics. Perhaps this merely suggests that the possible vascular regulatory mechanisms in the evolving stroke patient are as severely compromised in the diabetic as in the non-diabetic at the time of presentation with ischemic stroke.

PREVIOUS STROKES: The patients with histories of previous stroke might also represent a group with a particularly compromised cerebrovascular system. Table XVII lists the temporal profile of the 33 cases of stroke-in-progress who had past medical histories of stroke. Others have found a similar percentage of ischemic stroke patients with such previous histories.(19,24,45,53) Some authors have suggested that this history implies a worse prognosis.(10,24,30) Curiously, in the present study, the mean day of progression for these 33 cases was actually later, although the slight delay has no significance.

MEDICAL THERAPY: This research study was not designed to evaluate the effect of various modes of therapeutic intervention on the ultimate morbidity and mortality of strokes; nor was it established to examine the role of such intervention on the temporal profile of the acute event. In such a study, of course, strict attention would be given to randomized patient selection, uniform dosages of medication, the timing of administration with respect to initial onset, etc. Furthermore, progression must be carefully defined and clinically documented. Millikan has stressed that the results of such studies must always be in comparison with the study of the natural history of the disease.(149) With these criticisms in mind the effect of medical intervention on progressing stroke will be reviewed in the literature.

Medical therapy trials have primarily been directed toward halting edema formation or the ongoing clotting mechanisms. Both clinical trials and animal experiments have been carried out to alter progression,as well as investigate the pathogenesis of evolving stroke.

STEROIDS: The role of edema, or at least its amenability to the steroid therapy, is not apparently major. In a variety of animal models of ischemic infarction, steroids have been shown to be disappointingly ineffective in altering the mortality and morbidity.(126-129) The appropriateness of these various models for deriving inferences applicable to the clinical setting is discussed in an excellent review article.(130) In the study of steroids in the acute clinical setting of a stroke, Bauer and Tellez found steroids to be without effect on acute morbidity.(46) The autopsy review of Ng and Nimminnitya provides a possible explanation.(131) Edema may be without major effect on the patient's course, except in the case of massive infarct. However, this massive edema may be little affected by steroid administration.(132)

In Shaw's study of fatal stroke of sudden onset, involving the MCA, edema with midline shift was the common finding in patients dying in the first week.(133) Notable in their data is the observation that the rate of change of brain volume is greatest in the first 2 days after the initial onset of symptoms in these fatal strokes. Lee, _et al_. studied an animal model of acute stroke and provided a similar picture.(129) Describing the neurological deficits arising after occlusion of the MCA in the cat, they noted that the clinical presentation was quite uniform in temporal profile with the maximum deficit coming on day two after occlusion. This coincides with the time of maximum tissue edema.(134) Spontaneous resolution of the edema is noted to begin 3 to 5 days after occlusion

in the surviving animals.(135) In the primate model of MCA macroembolization, a similar temporal picture of increasing and decreasing edema is noted.(136) Whether this seemingly steroid-independent edema plays a major role in causing the progressing stroke picture or is merely a concomitant epi-phenomenon remains unanswered to date. Investigation of the brain tissue's inherent mechanisms for the production and elimination of this edema fluid may guide future therapy.

ASPIRIN: The institution of aspirin therapy in the acute setting has theoretical support. Mielke, et al., have shown that the onset of pronounced antiplatelet activity occurs within hours of the ingestion of even small doses of aspirin.(137) Further, Swank and Bartsch have reviewed the experimental evidence that platelet clumping in ischemic regions causes spreading of the ischemia through embolization into the local microvasculature.(138) Such embolization to leptomeningeal vessels from a slow-growing thrombus source was suggested on clinical grounds by Houser, et al. (52) to explain progression; fresh small vessel platelet aggregates in the context of progressing stroke have been found frequently at autopsy.(42) Alternately, Watts' experiments using autologous clot in dogs suggests that the release of chemical substances by platelets may widen the margin of ischemia by local vasospasm.(139) Serotonin may well be such a substance.(140)

Platelets have a suggested role in accelerating atherosclerotic plaque formation.(141) For several years platelet-fibrin emboli have been generally accepted as the common agents of TIA's.(142) The usefulness of anti-platelet drugs to prevent TIA's and strokes is currently under intensive investigation and the subject of several review articles.(143-145) These studies examine stroke prevention. They do not elucidate the possible role of continued platelet aggregation in the context of stroke-in-progress, an area for further study. Perhaps, the hypothesized local platelet accumulations,

or the numerous substances they release, are actually immune from or otherwise overwhelm any possible aspirin effects.(146,147) It may be beneficial to evaluate agents that counteract the effects of these released substances in the search for a method to halt progression.

ANTICOAGULATION: The literature does contain studies suggesting that anticoagulation favorably alters the natural course of progressing ischemic stroke. An early report by Fisher stimulated interest in anticoagulation.(13) He provided a personal series of the reversal of progressing stroke in 11 of 14 patients at the time oral or intravenous anticoagulant medication was added to their treatment programs. Furthermore, for unclear reasons, five of these improving patients had their anticoagulation therapy interrupted; three of this group subsequently deteriorated. He contrasted these encouraging results with the disappointing results found uniformly among patients who presented with completed strokes. Of course, this is a small, personally selected series without adequate controls.

Shortly after Fisher's report was published, several other series came out, again supporting the use of anticoagulants in the context of progressing thrombotic and also perhaps embolic stroke.(14,15,21,22,28,148) Based on these earlier studies and their own clinical experiences, several neurologists have more recently affirmed the belief that anticoagulants are often indicated to reduce mortality and arrest the progress of evolving stroke.(149-151) These authors temper their enthusiasm, acknowledging that the well-known multi-organ hemorrhagic complications of anticoagulation therapy severely limit patient selection. Adams and Victor simply state their own view of anticoagulation: "Anticoagulants also may halt the advance of a progressive thrombotic stroke, but not in all cases. In deciding whether or not to use anticoagulants, one faces the question of

where in the course of the stroke the patient stands when he is first examined. Will his course be benign or disastrous? And . . . there are no reliable rules for predicting this at the present time."(152)

Analysis of the data presented in Tables VI a-b shows that only those patients presenting to the Unit with TIA's had a significantly delayed mean time course of progression compared to those presenting with permanent deficits of any severity. Only a very few patients among those admitted in Class II-IV exhibited similarly late progression. Perhaps among the patients presenting with TIA's and a very few presenting with permanent deficits, some are manifesting a different mechanism; late progression might represent repeated stroke. In contrast the vast majority, those evolving within the first two or three days of onset, may be exhibiting the time course of evolution of actual cerebral tissue infarction. The patients exhibiting delayed progression may warrant a special therapeutic approach. For example acute anti-clotting therapy may be discovered to be a prophylactic measure against repeated stroke but not to be effective in the treatment of cerebral tissue under actual infarction. This hypothesis would explain the inconsistent effectiveness of anticoagulation to halt progression noted in the quotation from Adams and Victor.(152)

CHAPTER 9

SUMMARY AND FINAL CONCLUSIONS

This study was established to characterize the natural history of stroke-in-progress in a large population receiving similar care and evaluation. Among the 313 prospectively obtained records of thromboembolic stroke, in-hospital progression was observed in 105 cases. In this sub-population a characteristic time course of progression was documented. The mean day of progression occurred at 3.6 days with one third of the cases progressing on Day Two. Progression after a week was rare.

Neither the age nor sex of the patients affected this temporal profile. Furthermore, patients with a past medical history of cardiac abnormalities, hypertension, diabetes, or stroke showed no difference in time course. Seizure activity and cardiac dysrhythmias in the acute setting could not be implicated as contributing to progression.

The findings in a small group of patients suggested an unusual temporal profile. The group of patients hospitalized with TIA's was observed to show progression later than those admitted with neurological deficits of any severity. It is speculated that this group manifested a different pathophysiological mechanism, such as recurrent embolus or extension of thrombus, thus causing repeated stroke. Most patients showed evolution within the first two or three days, manifesting the evolution of the process of cerebral tissue infarction. It is suggested that the temporal profile of this process is independent of spontaneous systemic changes or manipulation. As a corollary, this suggests an explanation for the apparent success of the various uncontrolled therapeutic trials reviewed in Appendix I: If the therapy were begun on Day Two, progression after

its institution would rarely be noted, naturally.

Kennedy, *et al.*, have argued against the use of intensive care treatment of acute stroke, showing that early stroke mortality was not improved (153). Intensive care unit monitoring did not reveal any factors that might be corrected to alter the time course of evolving stroke. On the other hand, within such a unit the progression of signs and symptoms could be documented and the temporal profile defined in a population. This unit may serve as a model for the future evaluation of therapeutic attempts to alter the changes actively proceeding in ischemic cerebral tissue.

APPENDIX I

REVIEW OF THE LITERATURE

(1935) C. M. Aring and H. H. Merritt discuss progressing strokes in terms of the time course being of aid in distinguishing hemorrhagic strokes from thrombotic or embolic. In this autopsy series, a progressive time course was noted in 18.7% of one hundred-twelve cases of hemorrhage over periods ranging from one-half hour to ten days. In the two cases of progression among the one hundred six thrombotic strokes coming to autopsy, the time courses were seven hours and two days, respectively. Only one of the twenty-three embolic strokes progressed and over a one day period.(1)

(1948) N. C. Gilbert and G. de Takats examined one hundred twenty-one patients in their study of the effect of stellate block on altering the outcome of cerebrovascular accidents. In their evaluation of the natural history of strokes, they found twenty-eight of fifty-three cases of thrombotic strokes had a "gradual onset," as did four of fifty-three hemorrhage strokes, whereas all of the fifteen embolic strokes were "sudden." Unfortunately. they did not strictly define these time periods of progression. Interestingly, they also admit that "some patients with apoplexy improve spontaneously" which makes the value of a therapeutic intervention often unclear.(2)

(1951) H. C. Johnson and A. E. Walker culled from the literature one hundred-one cases of angiographically diagnosed thrombosis of the internal or common carotid artery and added six of their own cases. In their comment upon the clinical course, they grouped the presentations into:

"sudden catastrophic onset" (35%), "slowly progressive course" (25%), and "transient attacks" (40%). They also did not clearly define the time limits of these three groups. The "slowly progressive" group seems to include patients whose attacks spanned months. The "transient attacks" group includes cases where the deficits persist for weeks or months, even until another attack supervened.(3)

(1953) C. H. Millikan, J. S. Lundy, and L. A. Smith critically studied the effects of stellate ganglion block in acute focal cerebral infarcts. They remark that several authors in the literature note that improvement often follows an acute episode as part of the natural history of the disease process. They add that in many studies of the popular intervention of the early 1950's, the stellate block, "the assumption is made that whatever improvement occurred was a result of the procedure and would not have happened without the stallate block." They continue to say that there certainly is the need for "an article that adequately records observations made from day to day on a large number of patients having acute focal cerebral vascular lesions. Such observations are necessary, as a basis for comparison, when an attempt is made to evaluate a new method of treatment of this disease. It [is] obvious that a reasonably standard technique of caring for and observing the patients should be devised to which could be added any 'new treatment' to be evaluated." They do not establish such a study in this paper, giving only brief details as to the natural history of progression in twenty-nine patients. The onset of signs and symptoms is followed over just one day. From this limited study, they do conclude that an extremely rapid progression of the stroke over three hours or less foreboded a worse prognosis at the two week

evaluation time than did a stroke developing more slowly over a full day.(4)

(1953) C. H. Millikan and F. P. Moersch evaluate the time course of progressing strokes of the carotid circulation in ninety-three patients in a follow-up to the previous study. They only describe the population for the first twenty-four hours and again conclude that the more rapid the development of the stroke the graver the prognosis. They also remark that in those patients whose stroke evolves in more than six hours, almost one-half show improvement in condition by the end of two weeks. They therefore stress that carefully following the acute time course has long-term prognostic significance.(5)

(1954) M. Fisher presents data from four hundred thirty-two consecutive routine autopsies where he found twenty-eight cases of occlusion of one or both carotid arteries. It was noted to often be difficult to distinguish these occlusions as thrombotic or embolic. In his brief review of the clinical records, he comments that hemiplegia was the typical finding and "the hemiplegia came on slowly in a stuttering fashion over a period of a day or two." No comment is made as to how common was this "day or two" time course among the fatal stroke population nor any suggestion as to how common this time course is in comparison to a population not coming to autopsy.(6)

(1956)J.Webster, _et al_ present clinical data of seventy patients with arteriographically proven occlusion of the carotid system of whom fifty-seven had hemiparesis or hemiplegia. As to time course, they note that

fifty of the fifty-seven had an "abrupt" time course without further defining this time limit. No comment is made as to the time course of evolution of the remaining seven.(7)

(1956) A. A. Glynn presents a retrospective analysis of the recent natural history of three hundred-fifteen cases of thrombotic, embolic, or hemorrhagic strokes. He notes that 58% of the one hundred sixty-four thrombotic strokes evolved "suddenly," within a minute or two; 20% evolved in a "gradual" manner, over a few hours to days; while 13% came on during sleep and another 9% had an otherwise unknown time course. Among the seventy-three cases of hemorrhagic stroke proven by C S F examination or autopsy, 62% were "sudden," 18% "gradual" and 20% of "indeterminant" time course.(8)

(1956) K. Sastrasin presents sixty-five cases of carotid thrombosis demonstrated by arteriogram, surgery, or necropsy. He vaguely discusses the onset of symptoms: one class of twenty-four patients presented with "a sudden apoplectic attack with or without loss of consciousness." The other forty-one had "a progressive onset with intermittent attacks" only characterized that nineteen progressed within a three month period and the remaining twenty-two between three months to over five years.(9)

(1957) J. Rankin retrospectively analyzes the clinical presentation of two hundred forty-eight patients with cerebral vascular accidents. All types are grouped together. Of these, one hundred seventy-eight were admitted within twenty-four hours of the onset of symptoms. Unfortunately, there is no quantitative description of the time course of onset in any of these cases.(10)

(1957) J. Riishede discusses the onset of symptoms if fifty-six patients with thrombo-embolic strokes. Forty-five patients developed their symptoms and signs acutely; that is, within five minutes. Three were subacute, in more than five minutes but less than one hour. Eight were gradual in development in more than one hour with no upper limit of time specified. No comment is made as to the documentation of the time of initial onset, the frequency of repeat examination, nor the incidence and timing of improvement of signs and symptoms.(11)

(1958) S. O. Lindgren presents clinical data on sixty-five arteriographically and/or autopsy proven cases of occlusion of the internal carotid or middle cerebral artery. Of these sixty-five selected patients, 35% are reported as having an "acute, catastrophic onset of symptoms," 42% had "transient attacks with no or only slightly persisting symptoms after the first minutes or hours" and 25% had a "slowly progressive onset," in terms of weeks or months. It is unclear how soon after the onset of symptoms these patients were brought under medical evaluation nor when their symptoms reached the maximal point, and if and when recovery occurred. He does comment that improvement of symptoms in the acute stage usually starts after about two or three weeks.(12)

(1958) C. M. Fisher studies the use of anticoagulant therapy in the stroke-in-evolution. He provides data on fourteen treated and fourteen untreated patients. Among the treated group, three patients developed their maximal neurologic deficits within "a few days." Seven had steady downward courses over one to seven days. The difference in the nature of these time courses is unclear.

In the fourteen untreated patients, nine developed a severe stroke, seven of these within two weeks. Little additional characterization of the nature of evolution of these strokes is provided. No indication is made on how the evolving stroke population differs from the total stroke population. No indication is made as to how patients were selected for treatment nor exactly when the treatment was begun. The comparison, untreated cases were chosen because they were not anticoagulant candidates "for various reasons" and so are clearly not to be regarded as controls.(13)

(1959) C. E. Wells restricts his study to the natural history of embolic strokes only. He gives clinical data on fifty-three patients in which sixty-three probable embolic events were observed. Although embolic strokes are identified in part by the criterion of suddenness of onset, he does comment that embolic strokes may present with a stutteringly progressive onset. He gives no details as to the time course of development of signs and symptoms after embolism other than noting that of the fifty-three patients, sixteen died as the result of embolism "in an interval of two and one-half hours to two months after onset, thus adducing further evidence that cerebrovascular accidents rarely cause sudden death."(14)

(1959) A. B. Carter constructs a retrospective study of two hundred-nineteen patients with probable thrombotic-type strokes to compare the effects of stellate block, anticoagulation, and no treatment on the morbidity and mortality statistics over the one year follow-up interval. In reviewing the records of these two hundred-nineteen patients, he

distinguishes three types of clinical presentation: ninety-two cases were "acute," in which the symptoms reached their maximum at once or within six hours, seventy-two cases were classified as "doubtful," wherein the time course could not be obtained, and fifty-four cases were of the third type, labeled "ingravescent," in which the stroke evolved over more than six hours. This later, progressive group, comprised nearly one-fourth of his study population. In the paper, he suggests that this group with its more slowly evolving stroke process may well be manifesting a different pathophysiologic mechanism of, say, an extending or fragmenting thrombus or of the developing of a thrombus in patients whose initial symptoms were due to vascular insufficiency without actual clotting. It is to this group of patients with progressing strokes that Carter believes particular attention might profitably be given, as they may well receive singular benefit from anticoagulation. His small amount of autopsy data based on only four patients with ingravescent strokes does not point to an obvious, single mechanism; three cases showed complete carotid occlusion, but the other showed stenosis only.(15)

(1959) E. F. Vastola and A. Frugh examine the efficacy of anticoagulation in altering the clinical course of progressing strokes. They subclassify presenting lesions as "complete" versus "incomplete" by attempting to separate thirty cases of hemiparesis from twenty-five cases of hemiplegia. They also pay particular attention to the time after initial onset that the patients reached medical evaluation and treatment, realizing that in the evaluation of a treatment intervention early initiation of therapy may be a most important factor.

They studied no control patients from which the natural history might

be deduced. They do not clearly note how many of the patients with paresis progressed to plegia. They admit that no prior knowledge of the natural history of progressing strokes makes interpretation of anticoagulation trials difficult.(16)

(1959) A. J. Luessenhop discusses the role of surgical intervention in carotid artery occlusive disease. In his literature review of four hundred sixty-four proven cases, he adds twenty-two from his own experience. This is a highly selected stroke population, as all cases had proven carotid artery disease by arteriography, surgical exploration or post mortem examination. As this is a compilation of several authors' data, it is impossible to know how carefully the time of initial onset of symptoms was documented nor how closely and by what criteria changes in clinical course were ascertained. In spite of these shortcomings, Luessenhop attempts to classify the progression of symptoms into three categories, essentially those of Johnson and Walker discussed previously: "rapid onset of severe symptoms," "slowly progressive onset of symptoms," and "intermittent and immediately reversible." To these he adds a fourth group of patients whose histories include "associated symptoms" such as headaches, syncope or psychic changes that appeared well before the onset of clear motor or sensory deficits.

Among the four hundred sixty-four cases, Luessenhop identified three hundred eighty-four cases of "spontaneous occlusion," where the artery occlusion did not occur concomitant with or immediately following a craniocervical surgical procedure or trauma. In this literature summary, one hundred-eighty of the three hundred eighty-four cases were in the first category with the stroke reaching its maximal point within forty-eight hours of onset. There is no attempt to evaluate the time course more

acutely than within the two day block. Ninety-six patients developed their maximal deficit more gradually in more than two days and more frequently over weeks or months. Ninety-seven patients had the intermittent picture, where Luessenhop presents their stroke temporal profile in terms of the summation of individual episodes occurring over years. The remaining patients are in the associated symptom category; this allows for no evaluation of the temporal profile of symptoms and signs.

Of interest is the section of this paper discussing seventy-three patients who develop signs of cerebral ischemia iatrogenically following occlusion of the common or internal carotid artery for the treatment of an intercranial anneuryms, vascular anomalies or a arteriovenous fistulae. The onset of symptoms usually began immediately, as might be expected, although there was a delay in many patients with a small peak of patients having their episode some twenty hours out from the precisely known time of surgical occlusion. In these cases of surgical occlusion, approximately half had the occlusion removed in an attempt to reverse the neurologic deficit. The time of this intervention after the onset of symptoms was not stated, unfortunately. In this group 59% showed complete and rapid recovery within minutes to days, and another 16% showed gradual but incomplete recovery over the weeks to months of the follow up. In other words 75% had an improving course. Notable, however, is that in the other half of patients in which the surgical occlusion was not removed, 41% made a rapid and complete recovery in minutes to days, and 32% made a gradual but incomplete recovery over the weeks or months of followup, making a similar 73% with a "naturally" occurring clinical improvement.(17)

(1959) W. K. Hass and E. S.Goldensohn report on the clinical and par-

ticularly the electroencephalographic findings in the thirty-five patients with verified carotid occlusive disease that came to the Neurological Institute of New York between 1949 and 1957. The onset of symptoms was described as episodic (stuttering) in twenty-two patients, slowly progressive in ten and sudden and persistent in three. Their time classification is not further elucidated as to when the lesion became maximal, and if and when recovery occurred. Only two of the thirty-five patients cameto medical evaluation within the first week of the onset of symptoms, so that little reliable information on the natural history of early stroke is available fromthis study.(18)

(1959) L. J. Hurwitz, _et al_ study the accumulated records from the New York Hospital and Bellview Hospital of fifty-seven patients with occlusion of the carotid system as demonstrated by arteriography. The records of thirty-three patients were reported as showing a sudden onset of symptoms, thirteen were slowly progressive, two had a stuttering time course, three had their occlusion demonstrated in the investigation of TIA's, five had occlusion demonstrated incidently, and one had no record of the type of onset. They do not further define these terms nor give information as to the evaluation of the stroke other than to comment that there was no relationship between the mode of onset and the severity of presenting findings.(19)

(1960) C. H. Millikan, R. G. Siekert, and W. P. Whisnant classify the clinical presentation of occlusive carotid artery disease in terms of four different temporal and perhaps pathophysiologic categories: "(1) incipient or impending stroke, (2) advancing stroke, (3) completed stroke, and (4) completed stroke with evidence of further activity of the cerebral

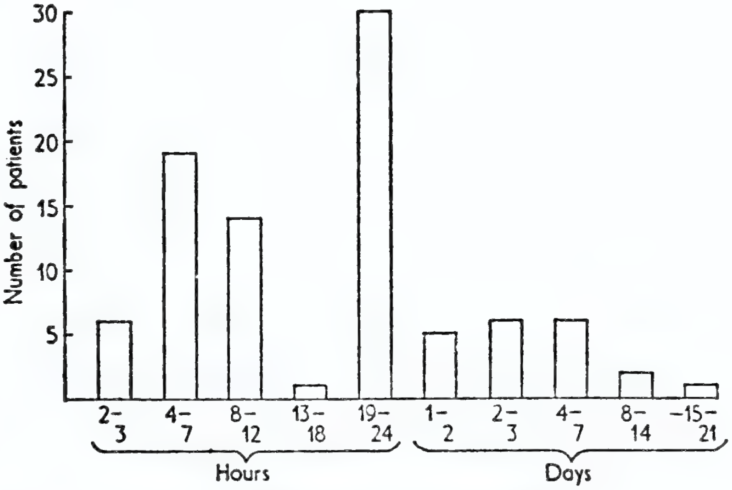
ischemic process." The second category represents in the stroke-in-progress. They speculate that several possible mechanisms may account for a progressive time course: " (1) stenosis-probably due to advancing thrombosis-is present, or (2) collateral supply has failed to provide the blood needed, or (3) prolonged inadequacy of supply produces defective function in more and more brain cells, or (4) a combination of these factors is existant." They add that "if thrombosis is progressing and causing infarction, worsening may continue by steps for a good many hours." Further they note, "in a small number of patients the clinical pattern forms gradually or progressively over many days to weeks." They also state "it is true, of course, that carotid thrombosis can become manifest by the very rapid onset (minutes) of maximal neurologic deficit." They note that characteristically: "after cessation of progression there may be a number of hours when the patients' condition changes little then unless damage has been extraordinarly severe, improvement begins. This phase of modest improvement is particularly characteristic of infarcts produced by thrombosis. The early and continuing improvement so common in cerebral thrombosis may be of importance in establishing the diagnosis particularly when there has been some reason to suspect the presence of a brain tumor or abscess."

As this paper attempts to review and evaluate the appropriateness of various modes of therapeutic intervention in active strokes, the authors quickly comment that the waxing and waning picture of the acute stroke and its lack of scientific study makes critical evaluation of a therapeutic modality nearly impossible. In their words, "the variability of the clinical course of actively advancing thrombosis makes indispensable the observation of a group of untreated patients for comparison of results before final evaluation of such treatment." Unfortunately,

this is only a review article and no data other than anecdotal description is given for examination of the temporal profile of the natural occurring stroke-in-progress.(20)

(1960) A. B. Carter again focuses on the "Ingravescent cerebral infarction." As earlier this is defined as a cerebral infarction taking more than two hours to reach its maximal deficit. In this study two hundred ninety-eight cases were examined from consecutive admissions below age eighty diagnosed as having a cerebral infarction. Of these thirty-six were excluded from the study as embolic strokes, leaving two hundred sixty-two thrombotic strokes in the population. Within this group ninety patients gave a history of an ingravescent cerebral infarction. Carter notes that among the patients excluded from ingravescent class because their progression was less than two hours were patients who awoke to find themselves paralyzed and those patients who were discovered unconscious and could give no history for progression, of course. Clearly, then, the frequency of ingravescent strokes is requisitely under-estimated in this study.

Most interesting is the finding in the ingravescent stroke population that the duration of the development of the neurologic lesion always fell within a time range of greater than two hours, by definition of course, to less than three weeks. Moreover, as is obvious from the reproduction of a bar graph in Carter's paper shown below, few patients were at the extreme time limits. In fact, in his study, fully one-third of the patients reached their maximal deficit in the nineteen to twenty-four hour interval.



Time of evolution of strokes.

This perhaps suggests that there is an intercerebral or intravascular event occurring at this characteristic time period to reverse the trend in progression. It also perhaps suggests that a therapeutic intervention done before this period may have a markedly different influence on the final outcome than does an intervention after the maximal deficit has been reached and the reversal trend has naturally become dominant.(21)

(1960) A. B. Carter submits a follow-up study to the last article in which he adds the records of the three years previous to those in the last study thus making a total of one thousand two cases of stroke of which four hundred twenty-five are thrombotic. However, quantitative data is only provided for the patients admitted between the years 1956 to 1958, as described in the previous study. No discussion is given to the hour

by hour progression of symptoms in this article. Little new insight is gained into the natural history of ingravescent strokes. Again, Carter speculates that the progressing stroke may reflect a special mechanism, perhaps a propagating thrombosis, the initiation of new thrombotic sites, or repeated distal embolism.(22)

(1960) J. Riishede, P. Ottosen and T. Søndergaard focus on the role of surgery in internal carotid artery occlusive disease in thirty-two patients presenting with apoplexy over age forty with unilateral or bilateral occlusion. The only comment as to the temporal profile is that it was "acute or subacute where initial impairment of consciousness was noted in half the patients in most instances was characterized by somulance, which decreased somewhat during the first hours or days follow-in the attack." They have difficulty recommending or speaking against endarterectomy, noting that the surgical risk is difficult to evaluate in a disease with an "unknown spontaneous course."(23)

(1960) N. J. David and A. Heyman analyze one hundred consecutive cerebral infarction admissions to a V.A. Hospital. They include any patient with an apparent thrombotic-type infarction occurring within two months of the day of admission; they have clearly limited their ability to observe acutely evolving processes. They, in fact, do not state specifically how many patients evolved while under hospital observation. Of the one hundred patients, fifty-five were labeled as having a stroke of "abrupt onset of symptoms while awake or during sleep." They do not elaborate on how abruptness was determined in the sleeping patient. In five patients the deficit was noted to develop in a gradual, stepwise progression over a period of twelve hours to several days. They

separately classify four patients who had transient symptoms following their initial infarction, as well as nineteen patients whose transient attacks preceeded the permanently disabling event. In neither group do they provide information as to the time course of development of the permanently disabling infarction.

Another thirteen patients were admitted with transient symptoms only. Another four patients were included in which no record of the time course of the ischemic event could be obtained. The subsequent results and discussion in this paper focus only on the long-term prognosis with no more comment as to the acute phase of progression or recovery.(24)

(1961) R. D. Adams, A. Torvik and C. M. Fisher retrospectively correlate the variably adequate hospital records with the post-mortem findings of thrombosis in an atherosclerotic brain artery or in the carotid or vertebral system in selected autopsy cases. They describe twelve examples of the lateral medullary infarction syndrome due to thrombosis of one vertebral or posterior-inferior cerebellar artery where reasonably complete clinical data were available. Reviewing the records, they find the deficit developed characteristically over a period of twelve hours to seven days. Most typically intermittent at initial onset with continued progression for one to ten days.

In thirteen cases of thrombosis of the basilar artery proven at autopsy the thrombotic process had clinically developed over a period of two to seventeen days with the tendency toward the shorter range of this time span. They note that "in several of these, a neurological symptom or syndrome, after a rapid onset, had improved for a number of days and then worsened before death."

Among the nineteen cases of unilateral or bilateral internal carotid artery thrombosis, six unmistakably showed a progression of symptoms of over four days to four weeks. In thirteen cases for which the history did not show progression in "several" were cases where the patient was found unconscious and so the temporal profile could not be ascertained.

They feel the progressing time course phenomenon may reflect a special mechanism and may be a guide to the search for effective therapeutic intervention:

"The second well known clinical feature of cerebral thrombosis is the relatively gradual development of the complete clinical syndrome over a period of hours, day or weeks or in rare instances months or even years; and it is this feature of the disease to which we now direct our attention. This progression may consist of a worsening of a given symptom, i.e., weakness of a limb, over an extended period of time, or of the addition of other symptoms referable to a disorder of neighboring structures. A worsening may in fact be followed by improvement and then intermittent progression or transient ischemic attacks one or several days later. This suggests that the patho-physiological change underlying transient ischemic attacks continues to operate during the evolution of a thrombotic stroke. In some cases, anticoagulants have seemed to smooth out this course, possibly indicating a suppression of this mechanism."

They attempt to further evaluate possible mechanisms at least in the fatal progressing strokes by a closer autopsy examination of the thrombotic material. The finding of the disintegrating leucocytes within the clot as well as the finding of endothelial cells and fibroblast invasion suggest that the thrombi are at least several days in the making. On

the other hand, they provide evidence that embolization distal to the thrombus also plays a role. They add that the neural elements themselves surely must have a variable lifespan after insult and so allow for an evolving picture.(25)

(1962) W. G. Hardy, et al examine the four year prognosis of one hundred fifty-three patients with arteriographically proved carotid artery occlusion. In this study little information is provided on the acute phase, as many patients had the onset of symptoms and initial progression outside of the hospital. Eighty patients had what is described as a "sudden" onset of symptoms with hospitalization occurring one day to sixteen years after onset. Only thirty-four patients were seen in the first week and a full twenty-one were not seen until a year or more after their stroke.

Fifty-two patients had an "episodic" onset with hospitalization from five days to seven years after the last episode. Most of these episodes were apparently TIA's. Fifteen patients had a progressive onset of symptoms over five days to a fourteen month course. Only one of these patients was seen within ten days of the onset of symptoms. Six patients presented to the hospital with associated complaints such as hearing the bruit.(26)

(1962) C. H. Edwards and N. S. Gordon examine endarterectomy for the treatment of carotid occlusion or stenosis in ninety-seven patients. The temporal profile was assessed by history and not by hospital observation. Among these patients, fifty-four patients had a stuttering onset of symptoms, thirty had a sudden onset of symptoms, and thirteen had a gradual progression. There was unfortunately no definition of these

terms, although "stuttering" apparently refers to a history of repetitive but transient episodes.(27)

(1962) R. Baker, <u>et al</u> present the outcome of a cooperative evaluation of anticoagulation, including the study of one hundred twenty-eight patients with stroke-in-progress. No information is provided on the actual time course of evolution. The only data provided is that of mortality with no mention as to the time of the occurrence of the final event after the onset of symptoms.(28)

(1963) E.S. Cooper, J. Ipsen, and H.D. Brown study the effect of cardiovascular disease has on the mortality statistics of 74 consecutive patients admitted with the clinical picture of an acute stroke. They included together thrombotic, embolic, and hemorrhagic strokes. All patients were followed for nine months. No information is provided as to when the acute episode began before hospital admission. They mention classifying patients according to the speed of onset of symptoms but do not provide the data in this paper.

Of these 74 patients, 64% died. No indication is made as to the role of the stroke in causing death; except to note that 92.3% of the patients admitted in deep coma died, whereas only 67% of the patients admitted "alert" were dead by the end of the nine month follow-up period. They also correlated increasing fatality figures with the greater severity of the paralysis. Patients with "grade 0-1" deficit had a 28.6% fatality rate, whereas those with "grade 3" paralysis had an 86.6% rate at nine months.(29)

(1964) A.B. Carter discussed mortality data in the acute setting of a "atheromatous cerebral infarction" (i.e. thrombotic stroke). Among the 612 patients studied in a chart review, 159 or 26% were dead within 4 weeks of the onset of the stroke. In agreement with others(4,5,12) Carter shows that the more rapid the development of symptoms the worse the chances for survival. In the study of 219 cases 47% of the patients developing symptoms in less than six hours were dead by four weeks, whereas only 21% of the patients with strokes evolving over more than six hours were dead. Carter is first to admit that his data are not ideal in that fully 1/3 of his study population were found unconscious or awoke paralyzed and so had unknown time courses of onset. 35% of the group were dead at the end of four weeks. In all three groups the peak of early death was between the third and tenth day.

Carter briefly remarks on the stroke morbidity in the acute setting, that the earlier the beginning of recovery the better the longterm prognosis: "If a patient is going to walk again there should be some movement of the legs within a few days of the stroke, and if the hand is ever going to be useful, movement of the finger and thumb must appear within the first two weeks." These comments are made without the presentation of supporting data.(30)

(1965) A. Silverstein and S. Hollin discuss the clinical presentation of internal carotid artery stenosis or occlusion as contrasted to middle cerebral artery stenosis or occlusion, as evidenced by fifty patients with each respective lesion demonstrated arteriographically. The clinical data for all one hundred patients was obtained from retrospective review of their hospital charts.

The onset of symptoms was described as quite sudden in forty-five patients with middle cerebral artery occlusion and in thirty-six internal carotid occlusion. In both groups this sudden onset of symptoms was frequently followed by rapid improvement but with subsequent intermittent episodes. This was noted in nine patients with middle cerebral artery disease and ten patients with internal carotid disease. They add that seven of the middle cerebral artery patients and nine of the internal carotid artery patients presented with an abrupt onset of symptoms with a progressive course. Five patients with middle cerebral artery disease and fourteen patients with an internal carotid artery disease had a gradual onset of symptoms. Unfortunately, they give no information as to the meaning of these terms. They do not state how soon after the initial onset of symptoms these patients came to hospital evaluation. Finally, there is no separation of suspected embolic strokes from thrombotic in the tabulation of the mode of onset. Despite these shortcomings, these authors come to the conclusion that middle cerebral artery occlusion more often presents abruptly, whereas internal carotid artery occlusion tends to have a progressive time course.(31)

(1965) R. G. Loscelles and E. H. Burrows retrospectively examine the acute clinical course in 59 cases of arteriographically proven stenosis or occlusion of the middle cerebral artery. Among these patients, three patterns of onset were discovered: 34 patients had what was called a "sudden or apoplectic" development of the maximum deficit; eleven patients had a "progressive" course where their condition steadily worsened over a few days; and fourteen patients had had a "stepwise" course with points of stability between episodes of progression. The authors note that all patients initially developed impairment of consciousness

which cleared rapidly--the exact time course not specified--in most patients who survived.(32)

(1966) J. Balow, M. Alter and J. A. Resch review 100 cases of cerebral thromboembolism. In all cases the onset of symptoms began within 1 month of hospital admission; at the time of admission all the patients had a stable or improving clinical course. By history only, then, 82 patients had a sudden onset of symptoms with the maximal neurologic deficit occurring within 1 hour. Included in the group, however, were all patients who gave a history of discovering their deficit upon awakening.

In the 18 remaining cases, the onset was more gradual, progressing to the maximum "after several hours or days." They mention that those individuals whose symptoms developed more gradually had a relatively higher chance of an improving course at the end of one month compared to those in the sudden onset of symptoms group. They give no quantitative data, adding that this conclusion was actually "not statistically significant."(33)

(1966) A. Torvik and L. Jörgensen review the hospital charts of 52 patients with occlusive disease anywhere in the carotid system, diagnosed among 994 consecutive routine autopsies. Of these,forty-one patients were symptomatic from the lesion and in thirty-three death was attributed to the occlusion. The length of survival from the onset of symptoms varied from eight hours to nine years. 1/2 of the patients died within the first 20 days.

On reviewing the histories, four types of onset were distinguished:

twenty-seven patients, or fully two-thirds of the cases, had a sudden onset of symptoms developing within minutes or "a few hours" and thereafter had a stationary or slowly worsening or improving course.

The second type was labeled "intermittent course," where the history was of sudden but transitory attacks occurring before the permanently disabling episode. Curiously, only one patient came to autopsy with this "characteristic" history for carotid artery disease.

Three patients had the third clinical course of repeated attacks lasting days with complete clearing or only minor residua between episodes.

The second largest group, comprising six patients, had the history of a step-wise progression of accumulating neurologic deficits. Unfortunately, the time course of the individual "steps" was not described.(34)

(1966) J. Marshall reviews the natural history of stroke in seventy-two patients who are arteriographically proven stenosis or occlusion of the internal carotid artery. Among the thirty-two patients with total occlusion, eighteen had the history of "completed stroke," meaning that a stroke reaching its maximum intensity in less than six hours and thereafter persisting over days or weeks with subsequent improvement usually stopping short of complete recovery. Seven of these thirty-two patients had a history of "progression," that is, symptoms developing gradually over more than six hours with no upper time limit specified.

Six of these thirty-two patients came to arteriography with a history of TIA's and one patient had a history of progressive mental deterioration only.

Among the forty patients with I C A stenosis, sixteen had the "completed stroke" history. Six had a history of "progression," sixteen

had T I A 's only and two in the group had arteriography for asymptomatic bruits.

In this retrospective chart review little clinical detail is available as to the acute time course of neurologic changes. Marshall notes only that one patient with occlusion and four patients with stenosis died in the "immediate" period without stating the exact time relationship of death to the initial onset of symptoms, admission to the hospital or date of arteriography.(35)

(1966) W. M. Lougheed, R. G. Elgie and H.J.M. Barnett report on the arteriographic and clinical findings on 109 patients undergoing carotid endarterectomy. Eight patients with internal carotid artery occlusion and four patients with stenosis were described as having a gradual, step-like progression of focal cerebral symptoms over a period of "hours or occasionally over a few days." In this paper they conclude: "The likelihood of restoring flow and the benefit to individual patients are maximal during the first few hours to days after occlusion of the artery. Although the best results will be obtained in patients presenting with transient ischemic attacks or strokes-in-evolution, surgical reconstruction should be attempted in some patients with completed strokes." Yet they also admit "The postoperative assessment of patients with completed strokes is extremely difficult in view of the natural history of improvement without definitive treatment in patients surviving the initial insult." They, however, do not give any details as to the time course of evolution or recovery of the individual cases studied. Surely, the natural history of progressing stroke is even less clearly known.(36)

(1967) C. M. Fisher and A. Pearlman present sixteen cases of cerebral embolism. Twelve of these cases were evaluated pathologically. The cases were collected over some twelve years for their unusual feature of a gradual or stepwise onset of symptoms in all sixteen cases. The authors speculate that this unusual time course in embolic strokes may reflect the effect of emboli in the bloodstream as they "gyrate, twist, and change shape conceivably straddling bifurcations temporarily or partially entering the side branches of a vessel,"or by, "the arrest of embolic material,. . . resulting in cerebral ischemia which was reversed by virtue of collateral blood flow entering the compromised territory." This paper is only a series of case reports primarily with autopsy follow-up data, so no accurate determination as to the incidence of progressing embolic stroke can be made.(37)

(1967) P. Bradshaw and E. Casey reviewed the records of forty-seven patients, forty-five of whom were under age sixty-five, with arteriography demonstrated lesions of the internal carotid artery. Of these patients selected for arteriography, thirty-three had a history of TIA's. Eleven had a sudden stroke. Three had ingravescent hemiparesis "which had increased during a period of twenty-four hours or more." No other comment is made as to the initial history of the stroke in this selected population.(38)

(1969) J. Marquardsen retrospectively studied the clinical course of 769 patients with any type of cerebral vascular accident. 80% of these patients were under hospital observation within twenty-four hours of the onset of symptoms. Only 8% are included in the study who were seen after three days from the beginning of symptoms.

In this study, 40.3% of the males and 31.8%of the females died within the first week of symptoms. A full 65% of the patients admitted in deep coma died within the first twenty-four hours of onset. He adds with regards to predicting prognosis that "A higher degree of validity is, however, obtained when changes in the state of consciousness during the first twenty-four hours are taken into account." He noted, when gradually increasing impairment of consciousness was observed in thirty-four patients who were initially semi-comatose or drowsy; only two of these survived the first three weeks. Similarly, there were only four survivors among thirty patients who, after having been fully conscious on admission, became drowsy, or lapsed into coma during the first day in hospital. A somewhat lower mortality was found in the group of somnolent or semi-comatose patients in whom improvement of conscious level took place shortly after admission; eleven of twenty-eight such patients survived. For those who were in deep coma on admission, however, the prognosis remained grave even if some improvement took place after admission; survival was observed only once in eight cases of this category. The sole survivor was a seventy-two year old female who was admitted immediately after a convulsive seizure; she regained consciousness a quarter of an hour later and became well after a few days.

It should be noted that these early mortality data must have included many cases of hemorrhage. In fact, of the patients who were either comatose or semi-comatose on admission or lost consciousness during the first twenty-four hours; 153 came to autopsy. Of these, 115 cases were hemorrhagic strokes. No details on the time course of development of morbidity nor on the factors that influence its development and prediction of long term prognosis are presented.(39)

(1969) G. C. Flora, T. Omae, and K. Nishimoru present a paper of the "clinical profile of the stroke patient" in U.S. and Japanese populations. The patients were selected with apparent thromboembolic type strokes occurring within one month of hospitalization. In remarking on the acute time course, they note that 84% of the 145 U.S. patients had an acute onset; the remainder had a gradual onset. In the Japanese population, 63% of the 123 patients had a sudden onset; and the remainder were gradual. These two temporal categories were not clearly defined. The time course assessment was obtained by history only. They state that "In a large number of patients an accurate history of the patients' state at the onset of the cerebrovascular accident was not available. They note that one fifth of the patients had their stroke occur during sleep.(40)

(1969) S. Heyden and C. J. Gerber discuss the clinical course of progressing strokes in their review article on atherosclerotic cerebrovascular disease. They declare, with no literature or data substantiation, that: "In progressive stroke the neurologic deficit develops gradually in a period of hours to days. In most cases, careful observation reveals that there is a saltatory accretion of symptoms. Less commonly, the evolving stroke proceeds smoothly and gradually without periods of stabilization between episodes of impairment. . . The importance of identifying stroke in its early evolution rests on the fact that therapy may be effective if instituted immediately after onset."

These authors would clearly agree that the frequency and characterization of the timecourse of progressing stroke need investigation as do the possible factors that predispose and/or influence the outcome of this type of stroke, if rational therapeutic intervention is to be made

at an appropriate time.(41)

(1969) L. Jörgensen and A. Torvik re-examine the data of their 1966 study of 994 consecutive routine autopsies. This paper focuses on the clinical course as well as pathology in 320 patients with ischemic cerebrovascular disease. In this retrospective review of the records of patients coming to autopsy, the most common temporal profile of stroke symptoms was that of sudden onset developing over seconds to "a few hours." This course was noted in 83.3% of the 171 stroke cases for which adequate clinical records were available. These records were obtained in 126 patients. This sudden onset to maximal deficit was particularly characteristic of the autopsy verified embolic strokes, where it was noted in fifty-seven of the fifty-eight cases examined.

Of the thirty-two cases of non-sudden onset of symptoms, only one was thought to be embolic. On autopsy thrombi were found in eighteen cases of which only nine were at extracranial sites. All thirty-one non-embolic cases had evidence of severe atherosclerosis of the cerebral arteries. The authors intimate that these findings argue against the frequent use of surgical intervention in progressing strokes.(42)

(1969) J. Gilroy, M. L. Barnhart, and J. S. Meyer appraise the use of Dextran 40 in the treatment of acute stroke in 100 patients. Their population had the acute onset of the stroke twenty-four to seventy-two hours prior to admission without further worsening at the time of admission. These patients, then, apparently had completed strokes at the time of therapeutic intervention rather than "progressive" strokes, as stated.

In this study all patients with systolic blood pressure recordings over 180 mmHg, cardiac disease, or renal impairment were excluded from the study, surely making this a rather atypical stroke population. Fifty-four patients received no Dextran 40 and served as controls. At the ten day follow-up reevaluation thirty-one of this group were improved, eight were unchanged, seven were worse, and eight had died.(43)

(1971) J. Acheson prospectively follows 500 patients over a mean period of 4.6 years. Unfortunately, only 338 patients were observed as in-patients of whom only ninety-six were emergency admissions, so that the comments on initial onset of symptoms apparently are by history only. Acheson has some information regarding the mode of onset in 394 patients. Of these, 326 or 82.7% had the maximal deficit at the initial onset of the stroke. Of the remaining sixty-eight, twenty-six were noted as developing their stroke between six and 24 hours, 31 between one to two days and the remaining eleven in longer than two days with no upper limits specified. Using the chi-square test comparing the mode of evolution with the degree of disability assessed at three, six, and twelve month follow-up; Acheson found no significant association. She makes no comment as to age, sex, cardiac, or other factors that might have been an influence on mode of onset.(44)

(1973) A. Brodal presents a description of his own stroke which interestingly had a progressive time course with the maximal deficit more than a day in coming on and with subsequent early recovery obviously evident by the fifth day.(45)

(1973) R.B. Bauer and H. Tellez evaluate the use of dexamethasone in ischemic stroke patients who had the initial onset of their deficit less than forty-eight hours before admission and who all presented with some impairment of consciousness. In this randomized, double-blind study a total of twenty-six patients were in the placebo group and served as controls for monitoring the natural history of the ischemic process. In this study, involving so few patients; the placebo group, by chance, received a larger percentage of patients with more severe presenting deficits. In an attempt to adjust for this unevenness the authors present their data of daily neurologic evaluation scores for the treated and control groups after excluding all patients admitted semi-comatose. Therefore, the data presented is based on only twenty selected control patients. By the end of two weeks, fifteen of these patients had improved or were unchanged. Five had deteriorated; three of whom had died. Unfortunately, the day to day data is presented as group averages for the control and treated patients so that no insight is given as to the natural history of evolving stroke in the individual patient.(46)

(1974) S.Q. Shafer <u>et al</u> evaluate the stroke morbidity in 524 consecutive stroke admissions. The patient population was composed of Black inner-city residents. The first sentence of this article states: "on the first day after stroke, the chances for survival can be reckoned quite reliably." They do not explain how such predictions can be accurately made nor further comment on the temporal profile of the patients during this apparently helpful acute period for prognostic evaluation.(47)

(1974) J. F. Toole and A. N. Patel state without providing the supporting data: "In most instances, the neurologic deficit resulting from a cerebral infarct reaches its maximum within the first seventy-two hours. Old age, hypertension, coma, cardiorespiratory complications, anoxia, hypercapnia, and neurogenic hyperventilation are additional adverse prognostic factors, especially in the first forty-eight hours after cerebral infarct. In rare instances the development of massive cerebral edema leads to progressive deterioration and sometimes death.

Some improvement may be apparent after the first two weeks and by the end of twelve weeks the maximum recovery will be reached in most cases. With noticeably few exceptions, no further recovery should be expected after six to nine months."

These are statements of clinical impressions that clearly deserve further examination and quantification in order that the validity of assessing prognosis in the acute setting can be evaluated. Also, the early adverse prognostic factors must be separately evaluated in order to ascertain their relative influence and the value of possible therapeutic manipulation.(48)

(1976) C. M. Fisher writes a chapter on the natural history of middle cerebral artery trunk total occlusion based on the analysis of forty cases. No information is given as to the system of collection or account of the reliability of detail of these records. He does note that in thirty-eight cases the M C A occlusion was confirmed arteriographically and pathogically in two cases.

Focusing on the acute natural history of M C A occlusion, Fisher states, without specific data, that embolic M C A stroke "probably always develops in a few minutes and without prodromal warning." He adds, "a few instances of embolism have been preceded by several TIA's in quick succession over a short period (eg. eight hours) but not over days or weeks." He qualifies his statement additionally: "An occasional embolic stroke appears to have shown as much as six hours of slow progression before realizing its peak."

Among the forty cases in this study, twenty-three were thought to be thrombotic M C A strokes on the basis of known long occlusion of the artery or by post-mortem study. Of these cases, 65% had prodromal TIA's and 15% had a step-wise progression of symptoms. In other words 41% of the cases presented with early symptoms that gave the physician some time to attempt medical or surgical intervention. In the progressing stroke Fisher states: "When a persistant stroke appeared and began to evolve in a step-wise or progressive fashion, the duration of progression to a peak was two or three days; a brief period which would demand quick decisions if surgical intervention were entertained." Clearly, the need to identify a progressing stroke early and predict the severity and time of maximal deficit are of great importance, as is the isolation of possible factors influencing the time course of events.(49)

(1976) H.R. Jones and C.H. Millikan review the records of the patients who were admitted to the Mayo Clinic Cerebrovascular Hospital Service between 1967-1969 with the diagnosis of carotid system infarctiion. Only patients admitted within thirty-six hours of the initial onset of symptoms were included in the study. Patients with a history of TIA's

only, collagen vascular disease, bacterial endocarditis, or syphilis were excluded. The patients' clinical courses were recorded "daily or more often" with the results for the first week graphed as severity of deficit vs. day after admission.

Of the 220 consecutive ischemic strokes reviewed, 179 had carotid system lesions. In examining the clinical course over the first week 39% of these patients were unchanged. 35% of the patients had gradually improved. 19% had a progressing neurological deficit from the onset which stabilized within two days. 4% had the course of significant late worsening, after 48 hours of a stable or improving course; 3% of these cases of acute carotid system infarction had a remitting-relapsing course in the first thirty-six hours.

To focus on the thirty-four patients (19%) with a progressing course, they note that this included patients with focal and/or general worsening of symptoms. Twenty-one patients showed progression focally of whom seventeen had the loss within the first "few hours." The remaining thirteen of the total thirty-four had a deterioration in level of consciousness, beginning at the onset in eleven and within the first forty-eight hours in all thirteen. The distribution of times over which stabilization occurred was not delineated. There was no evaluation made of the age, sex, cardiac, bloodpressure, etc. make up of this group of progressing stroke patients that might distinguish it from the non-progressing population.

Eight cases of progressing stroke patients came to autopsy; in seven there was cerebral infarction with edema, convolutional flattening mid-line shift, uncal notching, and secondary brainstem hemorrhage. In this study these authors agree with their old opinion that the rapid

onset of symptoms in less than three hours forbodes a poor prognosis for recovery of function.(50)

(1976) J. Marshall writes a chapter titled "Stroke-in-Evolution," where he speculates several mechanisms whereby a stroke "unfolds slowly over several hours or even one or two days,...most commonly in a series of distinct steps, the exact time of each deterioration being readily recognized." He speculates on several mechanisms: Increasing thrombus formation on a atheromateous plaque may interfere with the blood supply beyond the ability for collateral compensation. Edema may cause a gradual increase in symptoms. He says this mechanism should be suspected when the temporal profile is of abrupt onset of a stroke, followed by a period of stabilization for one to two days after which there is a deterioration of both local and general signs. If gradually developing ischemia provides,at least in some cases, a totally independent mechanism for progression of the stroke than does edema formation, then these hopefully might be clinically distinguished and so therapy guided more logically.(51)

(1976) O.W. Houser, et al. review the arteriographic findings in seventeen cases of progressing stroke of 6.6% of the 256 surgical cases of carotid artery occlusive disease. Curiously, fifteen of the cases involved the left hemisphere.

From hemodynamic measurements made at surgery correlated with the arteriographic findings, these authors speculate a pathophysiologic mechanism for the progressing stroke temporal profile. They suggest that in the context of decreased arterial perfusion and inadequate collateral

circulation, progression may occur when the major contribution of leptomeningeal vessel perfusion over the convexities becomes impaired secondary to embolization from the diseased carotid system.(52)

(1978) J. P. Mohr, et al, present a prospective study of 694 hospitalized patients. The authors do not clearly state the relationship between the onset of stroke symptoms and the time of admission. In the 232 cases of large artery thrombotic stroke, 40% had a "sudden" onset, 34% had a "step-wise or stuttering" course, 13% had a "smooth or gradual" course, and another 13% had a "fluctuation" from normal to abnormal.

Of the 213 cases of diagnosed embolism only 79% had what was described as sudden onset of symptoms. 11% had a stuttering or step-wise progression, 5% had a smooth or gradual increase of symptoms, and another 5% had a fluctuating course. This suggests that "thrombo-embolism" may at times be a safer clinical diagnosis to provide.

Of the 115 cases of cerebral hemorrhage the onset was sudden in 34% of the cases, stuttering in 3%, and smooth or gradual in 63% of the cases. After admission 56% of the patients deteriorated of which one fourth died suddenly. The timing of this event after admission was not specified.

131 patients had small, deep brainstem infarcts, i.e. lacunes. 38% of these patients had a sudden onset of symptoms, 32% had a step-wise or stuttering course, 20% had a smooth or gradual course, and 10% had fluctuations. This is similar to the temporal distribution noted in the large artery thrombotic stroke patients. This paper is a prospective study of a large number of patients. Unfortunately, the authors do not clearly state the meaning of their descriptions of the onset of symptoms.

They also do not provide any information on the course of these patients, throughout their hospital stay, and its relationship to the onset of symptoms.(53)

APPENDIX II

STANDARD PROCEDURE FOR NEUROLOGIC EXAMINATION - STROKE UNIT

Guidelines for Neurologic Examination

1. Examinations are to be made hourly, if possible, but patients are not to be awakened from sleep routinely except at change of shifts. Unless specified otherwise, periods of sleep will be charted as "sleep."

2. All estimations of level of responsiveness should be with reference to the previous examination.

3. Functional Grade evaluation will be made at change of shifts on the basis of bedside nursing rounds attended jointly by both shifts of nurses.

I. MENTAL STATUS

The evaluation of MENTATION and LANGUAGE FUNCTION result from conversation with patients with questions specifically aimed at determining orientation in time, place, person; ability to perceive passage of time; ability to retain recent knowledge; capacity for abstract thinking.

Mental Status Scoring:

L.O.C.

Fully Awake	100
Awake, time disorientation, or mild confusion	75
Lethargic; or confusion, and time, place, person disorientation	50

Responds to deep pain stimulus only	25
Coma	0
Seizures	S

II. EXAMINATION SCHEME FOR APHASIA

1. DYSPHASIA

It is important before beginning the examination to ascertain whether the patient is suffering from confusion and if so, to what degree. Confusion results in defective comprehension and formulation of verbal symbols, the effect of which is to produce symptoms of dysphasia. Experienced observers may find it difficult to decide whether the amount of confusion presents sufficient evidence to account for the dysphasia observed.

In order to avoid as far as possible the effects of fatigue, examination of speech function in a patient suspected of dysphasia should be conducted at a separate interview, which should not occupy more than 15 to 20 minutes. The patient should be comfortable and at ease. The purpose of the tests should be explained to him in appropriate terms. Failure should be glossed over by means of sympathy and encouragement. He should not be allowed to persist to the point of exasperation or despair over a test at which he has already shown himself inadequate.

The simplest tests for routine use are as follows. The responses should be recorded in detail. They will indicate what tests might be of value in the further investigation of a given patient.

A. ABILITY TO UNDERSTAND SPOKEN WORDS

The patient is given a series of verbal commands - the first should be "Close your eyes," then "Take hold of my hand." If these requests are promptly and correctly obeyed, more complicated commands are given, namely, "Touch your nose" and "Touch your left ear." If these commands are adequately carried out, the next should be "Touch your right ear with the index finger of your left hand." If this is correctly performed, he is told: "When I put both hands in my pockets, but not before, hold up your left hand." The examiner should be careful not to indicate by gestures the desired response.

B. ABILITY TO UNDERSTAND WRITTEN WORDS

A series of written commands should be presented to the patient in the order of increasing complexity. The command should first be written in legible handwriting. If there is failure, it should be repeated in block capitals. The commands are -

Open your mouth.
Put out your tongue.
Put your hand on top of your head.
Point to your left eye.
Touch your right ear with your left thumb.
When I lift my right hand above my head, but not before, pick up a pencil (a common object).

C. ABILITY TO EXPRESS HIMSELF IN SPEECH

1. There is no formal test for this. It should be be observed and recorded. Note should be made of defective grammar and syntax, the occurrence of jargon and the capacity to finish sentences, as well as failure in the production of words. Encouragement to talk may be given in a variety of ways appropriate to the patient and his circumstances, ranging from "How are you today?"; "Where do you live?" to "Tell me about your accident"; ... "I hear you are interested in... (hobby or work); they tell me you are fond of ..."

   The examiner should behave naturally in this conversation making use of expression and gesture to provoke a reply.

2. Naming Objects: The patient is asked to name a series of common objects shown to him. Very slight degree of dysphasia may be revealed by these tests. The patient may name all objects correctly except one and that a very familiar one such as a pen, although able to describe it in terms of its use as "What you write with."

The objects shown should be in the following order, those easily named being mingled with those more difficult:

1. Penny
2. Button

3. Handkerchief
4. Pencil
5. Wrist watch
6. Fountain pen
7. Collar
8. Tobacco pouch or cigarette case
9. Counterpane or blotting paper
10. Pin
11. Cuff links
12. Paper
13. Toothbrush or waste paper basket
14. Electric torch
15. Ash tray

D. ABILITY TO EXPRESS HIMSELF IN WRITING

The patient is given pencil and paper and asked to write some account of the weather, of his own complaint, of recent news in the papers, or of the happenings of his daily life or previous occupation.

APHASIA SCORING

A. COMPREHENSION

1. Understands language normally - 100.
2. Able to point to objects named or written - not able to understand written language other than single names - Record as 75%.
3. Able to distinguish RIGHT from LEFT side, able to carry out oral instructions requiring discrimination of side and

two other movements, i.e., close eyes, open mouth, hold up left arm or put left hand on right eye. Record as 50% - no ability to read.

4. Follows simple oral instructions, i.e., open mouth, close eyes, but not able to read these instructions - not able to carry out two instructions, i.e., open mouth, hold up arm. Record as 25%.

5. No comprehension of oral language - no ability to imitate - 0.

B. EXPRESSION

1. Normal speech - 100
2. Speaks in phrases but hesitates and gropes for words - Record as 75%.
3. Names common objects correctly but unable to use phrases - Record as 50%.
4. Says only "yes" or "no" appropriately and points to common objects correctly - Record as 25%.
5. No oral speech or ability to write - 0.

III. MOTOR FUNCTION TESTING AND SCORING

Motor function must be judged quantitatively, i.e.:

Normal strength (100)

Ability to hold limb elevated briefly (75)

Ability to raise limb against gravity (50)

Ability to move limb but not move it from bed (25)

Paralysis or absence of all movement will be called (0)

IV. SENSORY FUNCTION TESTING AND SCORING

A. Pin Stick

Face)
)
Arm) Normal = 100
)
) Altered = 50
)
Leg) Absent = 0
)

B. Position Sense

Hand) Normal = 100
)
) Absent = 0
)
and) Inaccurate appreciation of movement at
)
) slow rate = 75
)
) Appreciate movement at fingers only with
)
Foot) wide range rapid movement = 50

Appreciate movement at wrist not at

fingers = 25

C. DSS - Double Simultaneous Stimulation: Touch corresponding parts of body on right and left sides.

1. If both sides are felt, record as R--L.
2. If only right side is felt, record R/L.
   If only left side is felt, record L/R.

D. Touch Localization: Compare ability to localize touch on affected side with ability on normal side.

1. If results are the same, record 100%.
2. If touch is located on correct parts of body, but not as precisely as normal side, record 75%.
3. If touch is recognized on appropriate limb, but not more precisely, record 50%.

4. If there is ability recognize touch in the affected side of the body, but no ability to locate it, record 25%.
5. If unable to recognize touch on affected side, record 0.

E. Visual Fields Examination

<u>Monocular</u> - unable to count fingers with either eye.

<u>Homonymous</u> - unable to count fingers in one visual field. (or no response to threat in one visual field.)

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